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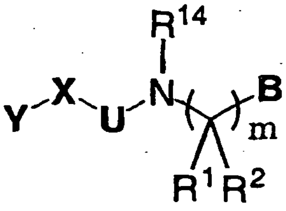
(54) Title: HETEROCYCLIC SIGNAL TRANSDUCTION INHIBITORS, COMPOSITIONS CONTAINING THEM

(57) Abstract

This invention concerns compounds for inhibiting intracellular signal transduction, especially intracellular signal transduction mediated by one or more molecular interactions involving a phosphotyrosine-containing protein. This invention also relates to pharmaceutical compositions containing the compounds and prophylactic and therapeutic methods involving pharmaceutical and veterinary administration of the compounds. The compounds are of formula (I) as defined herein.



(I)

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Heterocyclic Signal Transduction Inhibitors, Compositions Containing Them

Field of the Invention

This invention concerns a new class of compounds which have a broad range of useful biological and pharmacological activities. In particular, these compounds are useful for inhibiting intracellular signal transduction, especially intracellular signal transduction mediated by one or more molecular interactions involving a phosphotyrosine-containing protein. This invention also relates to pharmaceutical compositions containing the compounds and prophylactic and therapeutic methods involving pharmaceutical and veterinary administration of the compounds.

Background of the Invention

Cellular signal transduction, i.e., the series of events leading from extracellular events to intracellular sequelae, is an aspect of cellular function in both normal and disease states. Numerous proteins that function as signal transducing molecules have been identified, including receptor and non-receptor tyrosine kinases, phosphatases and other molecules with enzymatic or regulatory activities. These molecules generally demonstrate the capacity to associate specifically with other proteins to form a signaling complex that can alter cell activity.

Signaling proteins often contain domain(s) of conserved sequence which constitute catalytic domains such as kinase or phosphatase domains, or serve as non-catalytic modules that direct protein:protein or other inter- or intramolecular interactions during signal transduction. Such domains include among others, Src homology 2 ("SH2") and phosphotyrosine interaction ("PI") domains. SH2 and PI domains recognize, i.e., bind to, proteins containing characteristic peptide sequences which include one or more phosphorylated tyrosine ("pTyr") residues. Significant information related to such domains, proteins containing them, the production of proteins containing such domains (including protein fragments and fusion proteins), the characteristic peptide sequences which they recognize and the biological and/or clinical role played by the interactions of such proteins has been described in the scientific literature. See e.g. US 5667980, PCT/US97/02635 ("Cell-Based Assay") and WO 97/39326 ("In Vitro Fluorescence Polarization Assay") and references cited therein for additional background information on SH2 and PI domains, inhibition of intermolecular interactions mediated by such domains, assays and related topics.

The protein domains of the tyrosine kinase, Src, gave rise to the "Src homology" ("SH") nomenclature and illustrate this class of proteins. At least nine members of the Src family of tyrosine kinases have been identified to date in vertebrates including Src (alternatively known as c-src and pp60c-src), Fyn, Yes, Lyn, Hck, Fgr, Blk and Yrk. Sequence analysis of the Src tyrosine kinases reveals that each family member contains an N-terminal membrane anchor, a poorly conserved "unique" region of 40-70 amino acids, a Src homology 3 (SH3) domain of about sixty amino acids capable of protein-protein interactions with proline-rich sequences and a Src homology 2 (SH2) domain comprising about 100 amino acid residues which mediates binding of the Src family member of phosphotyrosine-(pTyr) containing peptides and proteins (reviewed in Superti-Furga, FEBS Lett. 369:62-66 (1995). Several cognate phosphoproteins known to bind the Src SH2 domain include middle T antigen, PDGF receptor, EGF receptor, and focal adhesion kinase (FAK). See Courtneidge et al, J. Virol. 65:3301-3308 (1991); Moi et al. EMBO J. 12:2257-2264 (1993); Luttrell et al. Proc. Natl. Acad. Sci. USA 91:83-87 (1994); and Xing et al, Mol. Biol. Cell 5:413-421 (1994). For additional information on other SH2 domains (including, e.g., ZAP-70, Syk, Shc, Tsk, Btk, VAV, Grb2, Crk, STATs) and PI domain-containing proteins, see WO 97/39326 and references cited therein.

The molecular structure of several SH2 domains has been solved and, in particular, the molecular structure of certain SH2 domains in complex with a phosphotyrosine-containing peptide or peptide analog has been elucidated. See Waksman et al, Cell 72:779-790 (1993); Xu et al. Biochemistry 34:2107-2121 (1995); Hatada et al, Nature 377(6544), 32-38 (1995). Whereas the general consensus sequence of Src family SH2-binding peptides, for example, comprises a pTyr-X-X-(Leu/Ile) motif, SH2 domain binding specificity is thought to be influenced significantly by the specific amino acids located carboxy-terminal to the pTyr residue. For example, the pp60c-src, Fyn, Lck and Fgr SH2 domains prefer the sequence pTyr-Glu-Glu-Ile. See Songyang et al, Cell 72:767-778 (1993). Crystallographic data concerning pp60c-src SH2 in complex with synthetic peptides has revealed, in particular, two important binding determinants for binding to phosphotyrosine-containing proteins or peptides: the phosphotyrosine binding site which is electropositive in nature such that phosphotyrosine binding is stabilized and the lipophilic binding site which stabilizes binding of pTyr+3 residues within the phosphotyrosine-containing peptides via hydrophobic contacts. Reviewed by Brown and Cooper, Biochim. Biophys. Acta 1287 (2-3):121-149 (1996).

Structural studies of phosphotyrosine-containing peptides complexed with isolated SH2 domains has provided information regarding the molecular interactions of peptide ligands with the SH2 domain peptidyl binding site. Recent attempts have been made to extrapolate these data to design novel peptide ligands and peptidomimetic agonists of SH2-

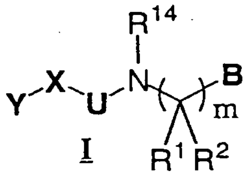
mediated signaling. For example, Plummer et al reported that incorporation of C-terminal D-amino acid residues to tripeptide SH2 domain ligands increases affinity relative to their L-amino acid-containing counterparts. See Plummer et al, Drug Design Discovery 13:75-81 (1996). Burke et al reported that hexapeptides containing difluoro-(phosphonomethyl)phenylalanine bound SH2 domains with high relative affinity compared to analogous pTyr peptides and were resistant to naturally-occurring cellular phosphatases. Studies of the pTyr residue of peptide agonists of the Src SH2 domain have shown that that phosphate ester is important for molecular recognition, and that significant loss in binding occurs when it is replaced with sulfate, carboxylate, nitro, hydroxy or amino groups. See Gilmer et al, J Biol Chem 269:31711-31719 (1994).

Many signaling pathways which play critical roles in disease processes are mediated by the binding of a phosphotyrosine-containing protein or protein domain with an SH2 or other protein receptor for a tyrosine-phosphorylated domain. Pharmaceutical agents which interfere with signaling mediated by such molecules, e.g., which interfere with the formation or stability of such signaling complexes, may be used for precise intervention in these complex biological processes in order to treat or prevent the diseases or pathological effects mediated by such signaling. Such interference may be achieved through a variety of mechanisms, including competitive inhibition of a phosphotyrosine-containing ligand with its receptor (e.g., with an SH2-containing protein), inhibition of phosphorylation of the tyrosine residue of such a ligand, inhibition of activation of a kinase which catalyzes the phosphorylation of a ligand in a signaling pathway, etc.

Compounds that can enter cells and block a signal transduction pathway of interest, such as an SH2-mediated pathway, would be of great interest as reagents for biological research and for pharmaceutical and veterinary uses.

Summary of the Invention

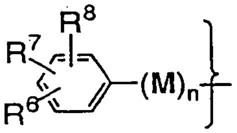
This invention concerns compounds of Formula I, or pharmaceutically acceptable derivatives thereof:



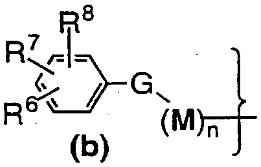
I

in which

Y is

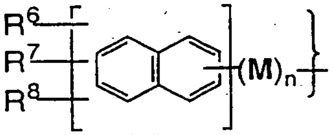


(a)



(b)

or



(c)

G is –O–, –S– or –**NR**–;

$\mathbf{R^6}$ comprises –**OR**, –$\mathbf{APO_3RR'}$, –$\mathbf{OPO_3RR'}$, –$\mathbf{ASO_3R}$, –$\mathbf{OSO_3R}$, –$\mathbf{ACO_2R}$, –**A**-tetrazole, –$\mathbf{ASO_2NRR'}$, –$\mathbf{ACOCF_3}$, –(C=O)**J**, –C(**R**)(**J**)(**K**) or –C(**Z**)(**J**)(**K**);

where each occurrence of **A** is independently a covalent bond, –**G**–**M**– or –$\mathbf{(M)_m}$–;

each occurrence of **M** is an independently selected, substituted or unsubstituted, methylene moiety, and any M-M' moiety may be electronically saturated or unsaturated and/or may be part of a 3-8-membered ring. Illustrative "M" moieties include –CH_2–, –CHF–, –CF_2–, –CHOH–, –CH(Me)–, etc.

Each **n** is independently 0, 1, 2, 3, 4 or 5 (in many embodiments n is 0, 1 or 2);

each **m** is independently 0, 1 or 2;

J and **K** are independently selected from the group consisting of –$\mathbf{APO_3RR'}$, –$\mathbf{OPO_3RR'}$, –$\mathbf{ASO_3R}$, –$\mathbf{OSO_3R}$, –$\mathbf{ACO_2}$R, –**A**–tetrazole, –$\mathbf{ASO_2NRR'}$, –$\mathbf{(M)_nNRR'}$ and –$\mathbf{(M)_nOR}$;

Z is a halogen (i.e., F, Cl, Br or I);

R^7 and R^8 are independently R, –CN, –NO_2, Z, J, –A(M)$_n$aliphatic, –G(M)$_n$aliphatic, –(M)$_n$$COCF_3$, –(M)$_n$OH, –(M)$_n$COOR, –A–(M)$_n$NRR', –G–(M)$_q$NRR', –(M)$_n$CHO, –A(M)$_n$N(R)(CO)R', –A(M)$_n$N(R)(CO)GR', –G(M)$_q$N(R)(CO)R', –G–(M)$_q$N(R)(CO)G'R', –A–(M)$_n$–CO–NRR', or –G–(M)$_n$–CO–NRR', where the aliphatic groups may be substituted or unsubstituted; or R^7 is a covalent bond to an R^4 substituent of **X** forming an aliphatic, aryl or heterocyclic ring of 4 to 8 atoms (including, for example a 5-membered nitrogen-containing ring of an indole moiety); additionally, R^7 and R^8 may be of the structure -(C=O)**R** so long as R is not alkenyl or alkynyl or **B** is not a thiazole.

Each occurrence of **R** (unnumbered) represents hydrogen or an aliphatic, heteroaliphatic, aryl, heteroaryl, (aryl)aliphatic–, or (heteroaryl)aliphatic– moiety, each of which (other than hydrogen) may be substituted or unsubstituted, e.g., with any of the various substituents listed, illustrated or otherwise disclosed herein. While each occurrence of "R" within a given compound is thus independently selected, where multiple R groups are depicted in the same figure or moiety, the various R groups are generally marked R, R', R" and so on, as a reminder that they may be the same or different. (The same is true in the case of numbered "R" groups and other variables such as "m", "n", "M", etc. where apostrophes are used for the same purpose. Note also that the *n* M groups in a "M_n" moiety may be the same or different from one another.)

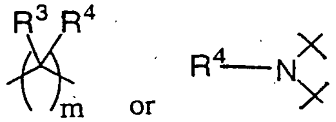
q is an integer from 1 to 8, and in many embodiments is 1, 2 or 3;

R^1 is hydrogen, aliphatic,–(M)$_n$–cycloaliphatic, –(M)$_n$–aryl, or –(M)$_n$–heterocyclic, each of which, other than H, may be substituted or unsubstituted (including, e.g. moieties such as –(M)$_n$$CO_2$R, –(M)$_n$C(O)NRR', –(M)$_n$Z, –(M)$_n$CN, –(M)$_n$tetrazole, etc.);

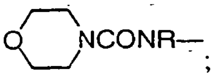
R^2 is hydrogen or substituted or unsubstituted aliphatic, which is optionally covalently linked with R^1 to form a ring;

or R^1 or R^2 are covalently linked either to **B** or a substituent of **B** to form a 4 - 10-membered, saturated or unsaturated, ring, or to the N depicted in Formula I above to form a 5, 6 or 7-membered, saturated or unsaturated, ring;

X is:



R^3 is hydrogen, R(CO)NR'–, **RR'**N(CO)NR''–, R'SO_2NR–, R'CSNR–, **RR'**'NCSNR''–, **RR'**'NSO_2NR''–, R'OCONR–, RR'N–, or



;

R^4 is hydrogen, aliphatic (which may be branched, unbranched or cyclic), cycloaliphatic–$(\mathbf{M})_n$–, aryl–$(\mathbf{M})_n$–, heterocyclic–$(\mathbf{M})_n$–, $\mathbf{RSO_2(M_n)}$– , $(CO_2R)(\mathbf{M})_{\mathbf{n}}$– or **(RR'N-CO)(M)**$_{\mathbf{n}}$, where the aliphatic, cycloaliphatic, aryl and heterocyclic groups are substituted or unsubstituted;

B is –{**HET**]$\mathbf{R^9R^{10}R^{11}R^{12}}$, where

HET is a heterocyclic moiety;

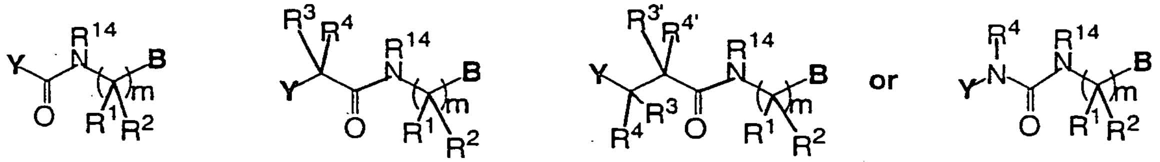
$\mathbf{R^9}$, $\mathbf{R^{10}}$ and $\mathbf{R^{11}}$ are independently **–(M)$_{\mathbf{n}}$Z**, **–(M)$_{\mathbf{n}}$R**, **–(M)$_{\mathbf{n}}$GR**, **–(M)$_{\mathbf{n}}$WR**, **–(M)$_{\mathbf{n}}$WGR, or –(M)$_{\mathbf{n}}$W–COR**, including, among others, moieties such as R, -OR,-SR, –CHO, –COR, -COOH (or amide, ester, carbamate, urea, oxime or carbonate thereof), -NH_2 (or substituted amine, amide, urea, carbamate or guanidino derivative therof), halo, trihaloalkyl, cyano, -SO_2-CF_3, -OSO_2F, -$OS(O)_2R$, -SO_2-NHR, -$NHSO_2R$, sulfate, sulfonate, aryl and heteroaryl moieties.

$\mathbf{R^{12}}$ is independently selected from **–(M)$_{\mathbf{q}}$Z**, **–(M)$_{\mathbf{n}}$R**, **–(M)$_{\mathbf{q}}$GR**, **–(M)$_{\mathbf{n}}$WR**, **–(M)$_{\mathbf{n}}$WGR**, and **–(M)$_{\mathbf{n}}$W–COR**;

R^{14} is R; and,

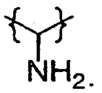
U and W are independently –CO–, –CS–, –M–, –SO–, or –SO_2–.

Compounds of Formula I thus include compounds having the following structures:

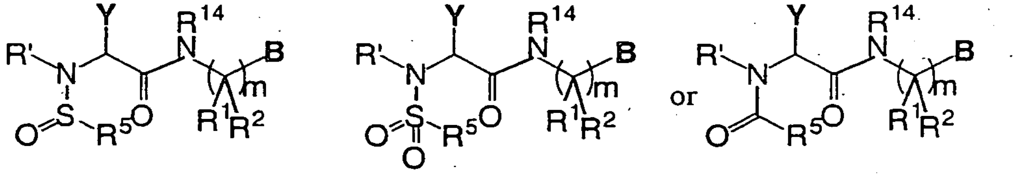


and comprise a number of subgenera of particular interest. Representative subgenera are illustrated in the examples which follow.

One subgenus includes compounds in which at least one R^4 moiety is H and at least one R^3 moiety is either H or NH_2. Compounds of the latter sort include those in which **X** is



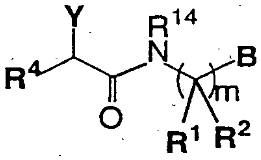
Also of interest are the subgenera of compounds in which the nitrogen atom of the moiety X is further elaborated, as depicted below:



where R^5 comprises a substituted or unsubstituted, lower (i.e., containing 1 - 8 carbon atoms) aliphatic or alkoxyl group, or is a substituted or unsubstituted –$(M)_n$–aryl or –$(M)_n$–heterocyclic (including e.g., substituted and unsubstituted phenyl or benzyl group, or a homolog and heterocyclic analog thereof, including e.g., 2-naphthyl, 3-indolyl, and 1-imidazolyl);

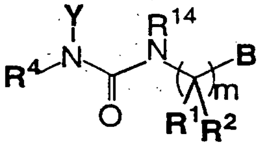
Such compounds are further illustrated by the subset thereof in which R^5 comprises –$(M)_nCH_3$, –$(M)_n$aryl, –$(M)_n$heterocyclic, –$(M)_nCN$, –$(M)_nCOOR$, where n is 0, 1, 2, 3, 4, or 5. For instance, in some such compounds R^5 is a substituted or unsubstituted methyl, ethyl, n–propyl, i–propyl, n–butyl, sec– butyl, t– butyl, n–pentyl, sec– pentyl, i-pentyl, cyclo pentyl, etc. or benzyl moiety. In other such compounds R^5 comprises $-(CH_2)_nCH_3$, $-(CH_2)(CH_2)_n$aryl, $-(CH_2)(CH_2)_n$heterocyclic, $-(CH_2)(CH_2)_nCN$ or $-(CH_2)(CH_2)_nCOOR$, where n again is 0, 1, 2, 3, 4, or 5. Examples of such compounds include those in which R^5 comprises $-CH_2CN$, $-(CH_2)CO_2R$, $-(CH_2)_2CO_2R$, $-(CH_2)_3CO_2R$, $-(CH_2)_4CO_2R$, where R is H, lower alkyl or benzyl and those in which R^5 comprises –O–(substituted or unsubstituted lower alkyl or benzyl).

Another subgenus of interest includes amides of the formula:



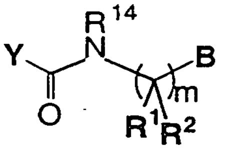
where **R^4** is hydrogen, substituted or unsubstituted aliphatic (which may be branched, unbranched or cyclic), substituted or unsubstituted aryl–$(\mathbf{M})_n$–, substituted or unsubstituted heterocyclic–$(\mathbf{M})_n$–, or $(CO_2R)(\mathbf{M})_n$–. Such compounds are illustrated by those in which **R^4** is $-(\mathbf{M})_n(CO)OR$, $-(\mathbf{M})_nSO_2R$, $-(\mathbf{M})_n(CO)N\mathbf{RR'}$, or $-(\mathbf{M})_n$(tetrazole), including, for example, compounds in which **R^4** is $-CH_2COOR$, $-CH_2SO_2R$, $-CH_2(CO)N\mathbf{RR'}$, or –tetrazole. Simple members of this subgenus are those in which the R group(s) of **R^4** is (are independently) H, lower alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tbutyl, etc.) or benzyl.

Another subgenus includes ureas of the formula:



where **R^1**, **R^2**, **R^4**, **R^{14}**, **Y** and **m** are defined as above. Thus, **R^4** may be simply H or may be a more complex **R^4** moiety such as are noted above.

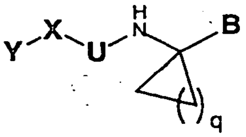
Another subgenus includes amides of the formula:



In many examples of the foregoing compounds, one or more R moieties (R', R" etc) are H. Also, in many compounds of interest, R^{14} is H.

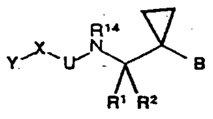
One subgenus of interest includes compounds of Formula I, including the examples described or illustrated above, in which **m** is 1, $\mathbf{R^1}$ is H, and $\mathbf{R^2}$ comprises H, $-(M)_nH$, $-(M)_n-$(substituted or unsubstituted lower alkyl), $-(M)_n-$(substituted or unsubstituted aryl), $-(M)_n-$(substituted or unsubstituted heterocyclic), $-(M)_n-COOR$, or $-(M)_n(CO)NRR'$. That subclass is illustrated by compounds in which $\mathbf{R^1}$ is H, and $\mathbf{R^2}$ is methyl, ethyl, i–propyl, n–propyl, n–butyl, isobutyl, n–amyl, sec–amyl, isoamyl, substituted benzyl, $-CH_2-$(3–indolyl), $-CH_2-$(4–imidazolyl), $-CH_2CH_2COOR$, $-CH_2CH_2CONH_2$, $-CH_2COOR$ or $-CH_2CONH_2$.

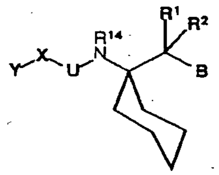
Another subgenus includes compounds of Formula I, including compounds of the sort described or illustrated above, in which $\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected, substituted or unsubstituted lower aliphatic groups, usually of 1 - 8 contiguous carbon atoms, or $\mathbf{R^1}$ and $\mathbf{R^2}$ are covalently linked to each other to form a ring, which may be a substituted or unsubstituted, aliphatic or heterocyclic ring or ring system (e.g. a bicyclic moiety), generally containing 3 - 10 annular atoms. Compounds containing an unsubstituted 3-10-membered ring are illustrated by the following formula, where q is an integer from 1 to 8:

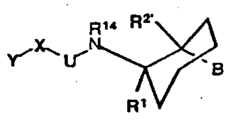


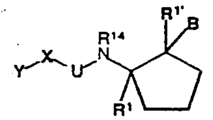
Another subgenus includes compounds of Formula I, including the examples described or illustrated above, in which **m** is 2, and each of $\mathbf{R^1}$, $\mathbf{R^{1'}}$, $\mathbf{R^2}$, and $\mathbf{R^{2'}}$ is independently selected from H, $-(M)_nH$, $-(M)_n-$(substituted or unsubstituted lower alkyl), $-(M)_n-$(substituted or unsubstituted aryl), $-(M)_n-$(substituted or unsubstituted heterocyclic), $-(M)_n-COOR$ and $-(M)_n(CO)NRR'$. In some such compounds, each of $\mathbf{R^1}$, $\mathbf{R^{1'}}$, $\mathbf{R^2}$, and $\mathbf{R^{2'}}$ is H.

Another subgenus of compounds of interest are compounds of Formula I, including the examples described or illustrated above, in which at least one of $\mathbf{R^1}$ and $\mathbf{R^2}$ is methyl, ethyl, i–propyl, n–propyl, n–butyl, isobutyl, n–amyl, sec–amyl, isoamyl, substituted benzyl, $-CH_2-$(3–indolyl), $-CH_2-$(4–imidazolyl), $-CH_2CH_2COOR$, $-CH_2CH_2CONH_2$, $-CH_2COOR$ or $-CH_2CONRR'$, or $\mathbf{R^1}$ and $\mathbf{R^2}$ are covalently linked to form a ring. In some cases, at least one of $\mathbf{R^1}$, $\mathbf{R^{1'}}$, $\mathbf{R^2}$, and $\mathbf{R^{2'}}$ is methyl, ethyl, i–propyl, n–propyl, n–butyl, isobutyl, n–amyl, sec–amyl, isoamyl, substituted benzyl, $-CH_2-$(3–indolyl), $-CH_2-$(4–imidazolyl), $-CH_2CH_2COOR$, $-CH_2CH_2CONH_2$, $-CH_2COOR$ or $-CH_2CONRR'$, or two of $\mathbf{R^1}$, $\mathbf{R^{1'}}$, $\mathbf{R^2}$, and $\mathbf{R^{2'}}$ are covalently linked to form a ring, which as in other cases, may be a substituted or unsubstituted, aliphatic or heterocyclic ring or ring system (e.g. a bicyclic moiety), generally containing 4 - 10 annular atoms. Compounds containing 3-, 5- and 6-membered rings are illustrated by the following formulas:

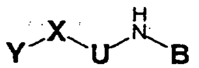




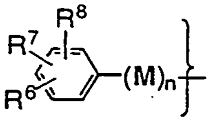


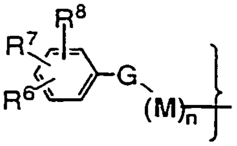


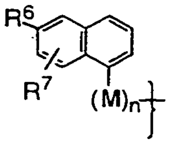
One subgenus of compounds of this invention, i.e., of compounds of Formula I, including among others the members of the various illustrative classes of compounds noted above, includes those compounds of Formula I in which **m** is 0:

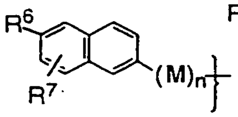


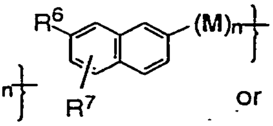
Compounds of Formula I, including, among others, compounds of the various subgenera described above, include those in which **Y** comprises



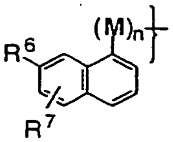








or



Such compounds in which $\mathbf{R}^6$ comprises –OR, –$\mathbf{APO_3RR'}$, –$\mathbf{OPO_3RR'}$, –$\mathbf{ASO_3R}$, –$\mathbf{OSO_3R}$, –$\mathbf{ACO_2R}$, –A-tetrazole, –$\mathbf{ASO_2NRR'}$, –$\mathbf{ACOCF_3}$, –C(**R**)(**J**)(**K**) or –C(**Z**)(**J**)(**K**); and, $\mathbf{R}^7$ and $\mathbf{R}^8$ are independently H, –CN, –NO_2, halogen, **J**, –A–$(M)_n$substituted or unsubstituted aliphatic, –$(M)_nCOCF_3$, –$(M)_nOH$, –$(M)_nCOOR$, –A–$(M)_n$**NRR'**, –$(M)_nCHO$, –A–$(M)_nN(R')(CO)R''$ or –A–$(M)_n$–CO–**NRR'** are of particular interest. This set of compounds is illustrated by those in which $\mathbf{R}^6$ comprises –OR, –$\mathbf{APO_3RR'}$, –$\mathbf{OPO_3RR'}$, –$\mathbf{ACO_2R}$, –$\mathbf{ACOCF_3}$, or –C(**R**)(**J**)(**K**); A comprises –$\mathbf{M_m}$– (e.g., –CH_2–, –CF_2–, –CHF– , –CHOH–, –CH_2CF_2–, etc), **–GM–** (e.g. –OCH_2–) or a covalent bond; each **R** and **R'** is H, or substituted or unsubstituted lower alkyl or substituted or unsubstituted benzyl; and, $\mathbf{R}^7$ and $\mathbf{R}^8$ are independently H, **J**, –A–$(M)_n$substituted or unsubstituted aliphatic, –$(M)_nCOCF_3$, –$(M)_nOH$, –$(M)_nCOOR$, –A–$(M)_n$**NRR'**, –$(M)_nCHO$, –A–$(M)_nN(R)(CO)R'$ or –A–$(M)_n$–CO–**NRR'**. For example, in some such cases, $\mathbf{R}^6$ comprises –OH, –$\mathbf{PO_3RR'}$, –$\mathbf{OPO_3RR'}$, –$CH_2\mathbf{PO_3RR'}$, –$CF_2\mathbf{PO_3RR'}$, –$OCH_2CO_2\mathbf{R}$, –$\mathbf{NRM_m}CO_2\mathbf{R'}$, –$CH_2CO_2\mathbf{R}$, –$CF_2CO_2\mathbf{R}$, –$CH_2SO_3\mathbf{R}$, –$CF_2SO_3\mathbf{R}$, –$CH_2COCF_3$, –$CF_2COCF_3$, –$CH(PO_3\mathbf{RR'})_2$, –$CH(OH)(PO_3\mathbf{RR'})$, –$CH(NH_2)(PO_3\mathbf{RR'})$, –$CH(CO_2\mathbf{R})_2$, –$CF(CO_2\mathbf{R})_2$, –$CH(PO_3\mathbf{RR'})(CO_2\mathbf{R''})$, –$CH(PO_3\mathbf{RR'})(SO_3\mathbf{R''})$, –$CH(PO_3\mathbf{RR'})(SO_2NH_2)$, –$CH(SO_2NH_2)_2$, or –$CH(SO_3\mathbf{RR'})_2$. Compounds in which $\mathbf{R}^6$ is –$\mathbf{NRM_m}CO_2\mathbf{R'}$ are illustrated by compounds in which **R** is H, –$\mathbf{M_m}CO_2\mathbf{R'}$, –$\mathbf{M_m}SO_2R''$ or another substituted or unsubstituted lower aliphatic moiety. In some such compounds, one or more of R, R' and R" in the $-PO_3\mathbf{RR'}$, $-OPO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-NHCH_2CO_2\mathbf{R}$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, $-CF_2SO_3\mathbf{R}$, $-CH_2COCF_3$, $-CF_2COCF_3$, $-CH(PO_3\mathbf{RR'})_2$, $-CH(OH)(PO_3\mathbf{RR'})$, $-CH(NH_2)(PO_3\mathbf{RR'})$, $-CH(CO_2\mathbf{R})_2$, $-CF(CO_2\mathbf{R})_2$, $-CH(PO_3\mathbf{RR'})(CO_2\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_3\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_2NH_2)$, $-CH(SO_2NH_2)_2$, or $-CH(SO_3\mathbf{RR'})_2$ moiety is H. In others, one or more of those R groups is $-(M)_m-CH_2\mathbf{Z}$, $-(M)_m-CH\mathbf{Z}_2$, $-(M)_m-C\mathbf{Z}_3$, $-R^{15}$, $-M-O-CO-OR^{15}$ or $-M-O-CO-R^{15}$, where Z is halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic. For example, in various embodiments, R^{15} is methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl, and M is CH_2, CHR (e.g. $CHCH_3$ etc.) and the like. Further illustrations include $-CH_2$-O-CO-OEt, –CH(Me)-O-CO-OEt, $-CH_2$-O-CO-t-butyl, etc.

In one subgenus of the foregoing compounds, $\mathbf{R^7}$ and $\mathbf{R^8}$ are both H. In another subgenus, $\mathbf{R^7}$ is J, $-\mathbf{A}-(\mathbf{M})_n$(substituted or unsubstituted aliphatic, aryl or heterocyclic), $-(\mathbf{M})_nCOCF_3$, $-(\mathbf{M})_nOH$, $-(\mathbf{M})_nCOOR$, $-\mathbf{A}-(\mathbf{M})_n\mathbf{NRR'}$, $-(\mathbf{M})_nCHO$, $-\mathbf{A}-(M)_nN(R)(CO)R'$, $-\mathbf{A}-(\mathbf{M})_n-\mathbf{NRR'}$ or $-\mathbf{A}-(\mathbf{M})_n-CO-\mathbf{NRR'}$; and $\mathbf{R^8}$ is H. The latter subgenus is illustrated by compounds in which $\mathbf{R^7}$ is lower alkyl, lower alkenyl, –OH, $-NH_2$, $-NO_2$, –CN, –NHR, –NHCOR, –CHO, $-CH_2CHO$, $-PO_3\mathbf{RR'}$, $-OPO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-NHCH_2CO_2\mathbf{R}$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-SO_3\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, $-CF_2SO_3\mathbf{R}$, $-COCF_3$, $-COCH_2F$, $-COCF_2H$, $-CF_2COCF_3$ or $-SO_2NH_2$. In some such compounds, one or both of R and R' in $-PO_3\mathbf{RR'}$, $-OPO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-NHCH_2CO_2\mathbf{R}$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-SO_3\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, or $-CF_2SO_3\mathbf{R}$ is H. In others, one or more of those R groups is $-(M)_m-CH_2Z$, $-(M)_m-CHZ_2$, $-(M)_m-CZ_3$, $-R^{15}$, $-M-O-CO-OR^{15}$ or $-M-O-CO-R^{15}$, where Z is halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic. For example, in individual cases, R^{15} is methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl, and M is CH_2, CHR (e.g. $CHCH_3$ etc.) and the like.

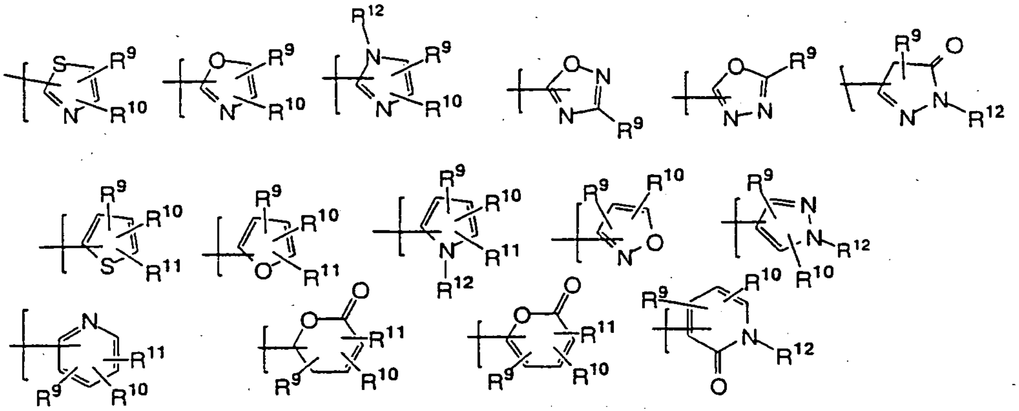
In an illustrative subgenus, $\mathbf{R^6}$ comprises $-\mathbf{APO_3RR'}$ (e.g., $-OPO_3H_2$) and $\mathbf{R^7}$ is $-\mathbf{A}-(\mathbf{M})_n$substituted or unsubstituted aliphatic.

In another subgenus, $\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from **J** and **K**.

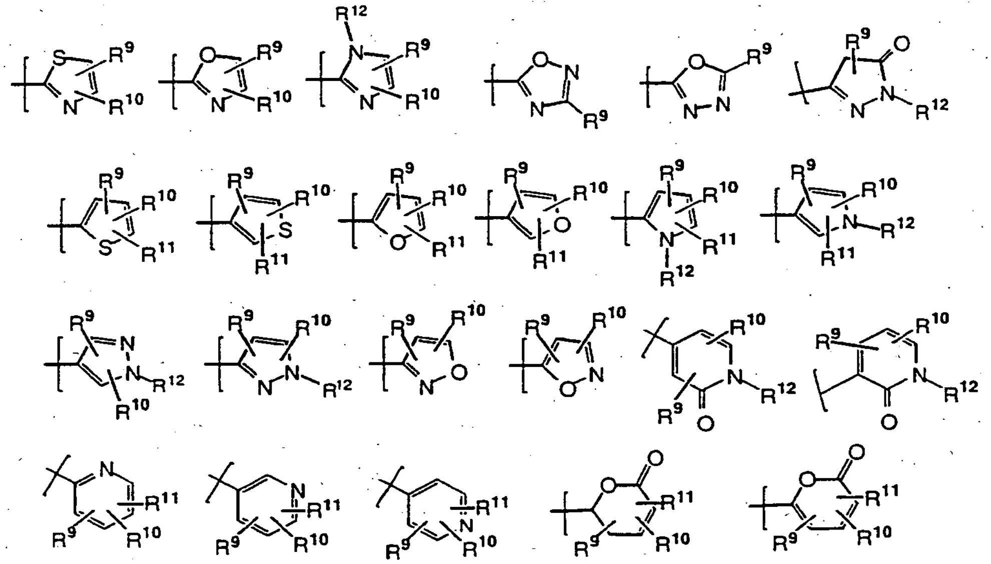
In another subgenus, $\mathbf{R^6}$ is $-C(\mathbf{R})(\mathbf{J})(\mathbf{K})$. Illustrative compounds of this subgenus include those in which $\mathbf{R^6}$ is $-CH(\mathbf{J})(\mathbf{K})$ and those in which $\mathbf{R^6}$ is $-C(\mathbf{R})(PO_3\mathbf{R'R''})(\mathbf{K})$. The latter compounds are illustrated by embodiments in which none, one, two or three of the R groups of the $-C(\mathbf{R})(PO_3\mathbf{R'R''})(\mathbf{K})$ moiety are H.

As in previously mentioned cases, compounds of this invention which contain a moiety J, e.g., compounds of Formula I in which $\mathbf{R^6}$ is $-C(\mathbf{R})(\mathbf{J})(\mathbf{K})$, include among others embodiments in which one or both of R and R' (e.g., of a $-PO_3\mathbf{RR'}$ moiety) are R^{15}, $-(M)_m-CH_2Z$, $-(M)_m-CHZ_2$, $-(M)_m-CZ_3$, $-M-O-CO-OR^{15}$ or $-M-O-CO-R^{15}$, where Z is halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic (e.g., methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl), and M is CH_2, CHR (e.g. $CHCH_3$ etc.) and the like.

The compounds of Formula I, including the various subgenera and illustrative examples described above, all contain a heterocyclic moiety, **B,** as that term is defined below and as is illustrated by the following group:



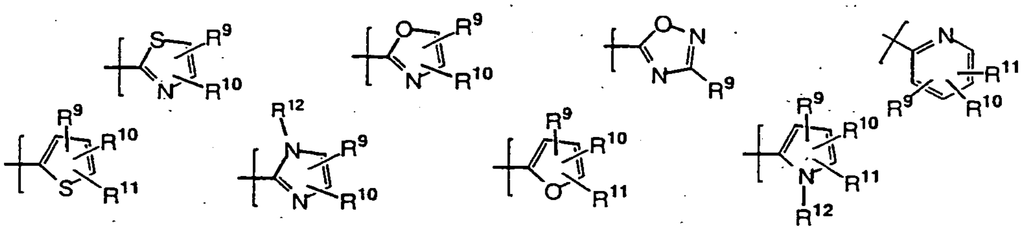
including, among others, the following specific cases



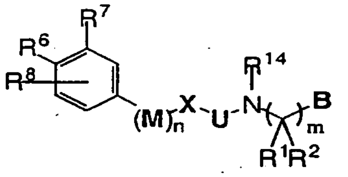
wherein each of R^9, R^{10} and R^{11} is independently **Z**, **R**, **–GR**, **–COR**, **–CO$_2$R**, or **–(M)$_n$W–NRR'** and R^{12} is independently selected from **–(M)$_q$Z**, **–(M)$_n$R**, **–(M)$_q$GR**, **–(M)$_n$WR** , and **–(M)$_n$WGR**. In some embodiments, one or more of the **R**, **R'** and **R"** groups of R^9, R^{10} and R^{11} comprise a halo, hydroxy, aliphatic, amino, amido or sulfonamido moiety. In some embodiments, one or more of R^9, R^{10}, R^{11}, and R^{12} is a substituted aliphatic moiety containing at least one substituent selected from substituted or unsubstituted cycloaliphatic, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, **–COR**, **–CO$_2$R**, **–CO–NRR'**, and **–OR**. In some embodiments of particular interest, one or more of R^9, R^{10}, R^{11}, and R^{12} comprises **–(M)$_n$**(cycloaliphatic),

$-(M)_n$(substituted or unsubstituted aryl), $-(M)_n$(substituted or unsubstituted heteroaryl), $-(M)_nCHO$, $-(M)_nCONH_2$, $-(M)_nCSNH_2$, $-(M)_nSONH_2$, $-(M)_nSO_2NRR'$, $-(M)_nOR$, $-(M)_n$(lower aliphatic), $-(M)_n-C(OR)R'R''$, or $-(M)_n-C{=}CRR'$. (In examples in which $\mathbf{R}^{12}$ is $-(M)_nOR$, **n** is 1 or greater.) For example, in some cases, one or more of $\mathbf{R}^9$, $\mathbf{R}^{10}$, $\mathbf{R}^{11}$, and $\mathbf{R}^{12}$ comprise methyl, $-(CH_2)_qR^{13}$ where q is 1–8 and R^{13} comprises methyl; i–propyl; i–butyl; t–butyl; cycloaliphatic; phenyl; substituted phenyl; naphthyl; substituted naphthyl; a 5, 6 or 7–membered heterocyclic ring or a bicyclic heterocylic moiety. In some cases, $\mathbf{R}^{12}$ comprises a formyl group on a ring nitrogen. Possible substituents on the **R**, **R'** and **R''** groups include, among others, halo, hydroxy, alkyl, amino, amido and sulfonamido moieties. Other potential substituents are as disclosed elsewhere herein, including in the numerous specific examples.

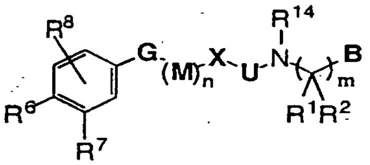
Compounds of particular interest include those in which **B** is selected from the following:



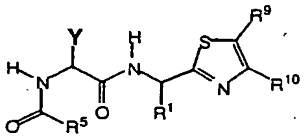
From the perspective of **Y** moieties, compounds of particular interest include those compounds of Formula I, including those of the various subgenera and examples herein, which have the following structures:



- and -



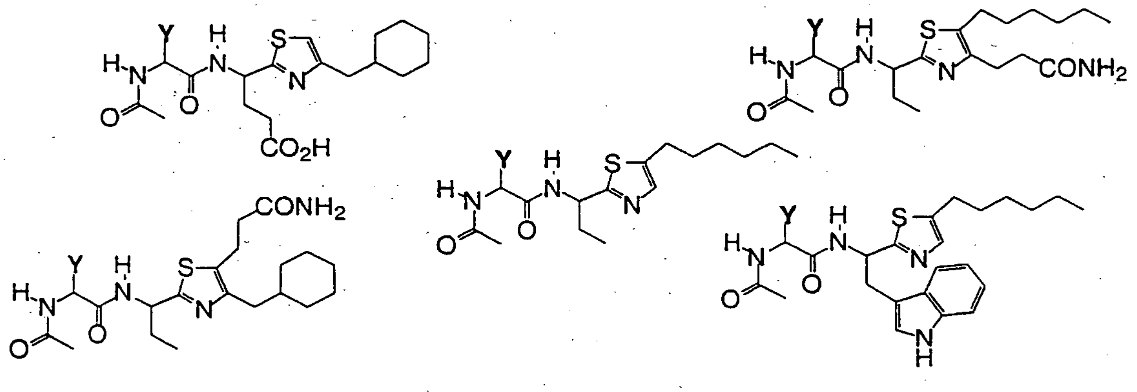
One subgenus of compounds of Formula I which is of particular interest includes thiazoles of Formula II:



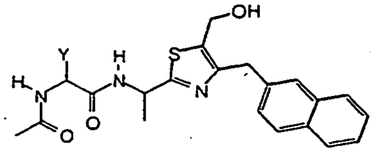
II

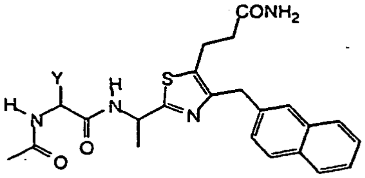
where R^1 and R^5 each comprise an independently selected, substituted or unsubstituted lower aliphatic moiety, and R^9 and R^{10} are each independently selected from H. and a substituted or unsubstituted lower aliphatic moiety.

This subgenus is illustrated by compounds of Formula II in which $\mathbf{R^1}$ comprises a linear, branched or cyclic lower aliphatic moiety, $-(CH_2)_nCOOH$, $-(CH_2)_n$aryl (substituted or unsubstituted) or $-(CH_2)_n$heterocyclic (substituted or unsubstituted); $\mathbf{R^5}$ comprises a linear, branched or cyclic lower aliphatic moiety; and $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently selected from H; linear, branched or cyclic lower aliphatic; $-(CH_2)_nCOOR$; $-(CH_2)_nCONRR'$; $-(CH_2)_n$cycloaliphatic (substituted or unsubstituted); $-(CH_2)_n$aryl (substituted or unsubstituted) or $-(CH_2)_n$heterocyclic (substituted or unsubstituted). For example, in some cases, $\mathbf{R^1}$ comprises a linear, branched or cyclic lower aliphatic, $-(CH_2)_2COOR$, $-(CH_2)_2$aryl (substituted or unsubstituted) or $-(CH_2)_2$heterocyclic (substituted or unsubstituted); $\mathbf{R^5}$ comprises a linear, branched or cyclic lower aliphatic; and $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently selected from H; linear, branched or cyclic lower aliphatic; $-(CH_2)_2COOR$; $-(CH_2)_2CONH_2$; $-(CH_2)$cycloaliphatic (substituted or unsubstituted); $-(CH_2)$aryl (substituted or unsubstituted) or $-(CH_2)$heterocyclic (substituted or unsubstituted). Thiazoles of Formula II, e.g. compounds such as those shown immediately below, may be useful as inhibitors of cellular signaling mediated by Src or Src family kinases, and thus may be useful in treating diseases such as osteoporosis and other bone resorptive disorders in patients in need thereof.



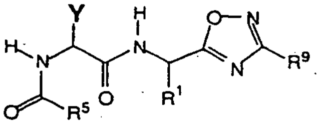
The following thiazoles further illustrate the compounds of Formula II:





and may be useful as inhibitors of cellular signaling mediated by ZAP-70 or ZAP-70 family kinases, and thus may be useful in treating or preventing an inflammatory response in patients in need thereof. Such compounds may be used for example as immunosuppressants in patients who are going to receive, or have received, an organ or tissue transplant or in patients suffering an autoimmune disorder.

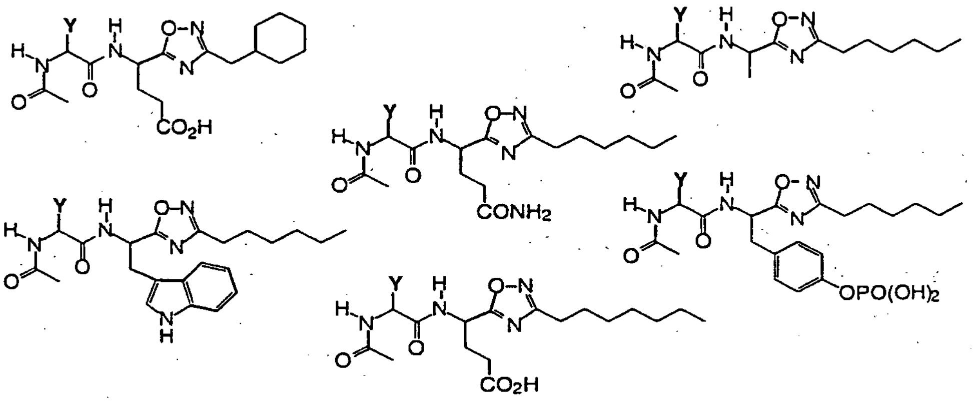
Another subgenus of compounds of Formula I which is of particular interest includes oxadiazoles of Formula III:



III

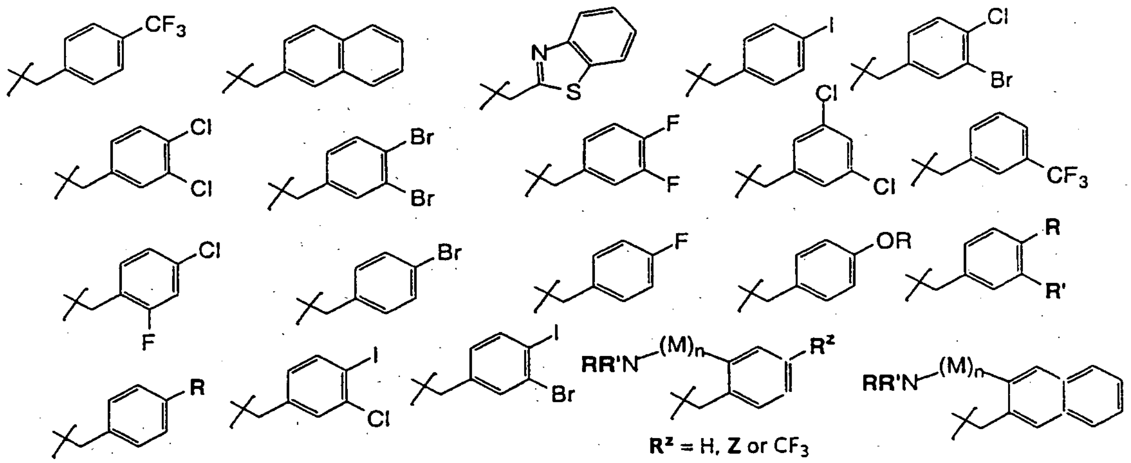
where R^1 and R^5 each comprise an independently selected, substituted or unsubstituted lower aliphatic moiety, and R^9 comprises H or a substituted or unsubstituted lower aliphatic moiety. In some cases, $\mathbf{R^1}$ comprises a linear, branched or cyclic lower aliphatic, $-(M)_n$aliphatic (which may be substituted or unsubstituted), $-(M)_nCOOR$, $-(M)_nOR$, $-(M)_n$aryl (which may be substituted or unsubstituted) or $-(CH_2)_n$heterocyclic (which may be substituted or unsubstituted); $\mathbf{R^5}$ comprises a linear, branched or cyclic lower aliphatic; and $\mathbf{R^9}$ comprises H; linear, branched or cyclic lower aliphatic; $-(M)_nCOOR$; $-(M)_nCONRR'$; $-(M)_n$cycloaliphatic (which may be substituted or unsubstituted); $-(M)_n$aryl (which may be substituted or unsubstituted) or $-(M)_n$heterocyclic (which may be substituted or unsubstituted). In its simplest form, M is CH_2. For example, in some embodiments, $\mathbf{R^1}$ comprises a linear, branched or cyclic lower aliphatic, $-(CH_2)_2COOR$, $-(CH_2)$aryl (substituted or unsubstituted) or $-(CH_2)$heterocyclic (substituted or unsubstituted); $\mathbf{R^5}$ comprises a linear, branched or cyclic lower aliphatic (substituted or unsubstituted); and $\mathbf{R^9}$ comprises H; linear, branched or cyclic lower aliphatic; $-(CH_2)_2COOR$; $-(CH_2)_2CONH_2$; $-(CH_2)$cycloaliphatic (substituted or unsubstituted);

–(CH_2)aryl (substituted or unsubstituted) or –$(CH_2)_2$heterocyclic (substituted or unsubstituted). Oxadiazoles of Formula III may be useful as inhibitors of cellular signaling mediated by Src or Src family kinases, and thus may be useful in treating diseases such as osteoporosis and other bone resorptive disorders in patients in need thereof. Oxadiazoles of Formula III are further illustrated by the following types of compounds:

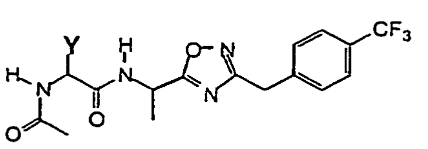


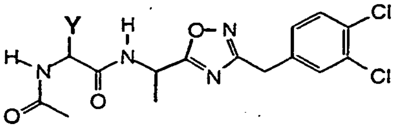
Various compounds of Formula I (including each of the foregoing subgenera thereof) containing a substituent $\mathbf{R^9}$ which comprises –$(M)_n$–aryl (which may be substituted or unsubstituted) or –$(M)_n$–heterocyclic (which may be substituted or unsubstituted). Again, in its simplest form, M is CH_2.

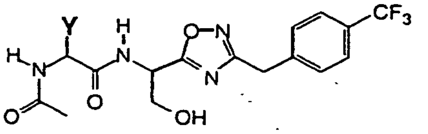
Such $\mathbf{R^9}$ moieties are illustrated by the following:

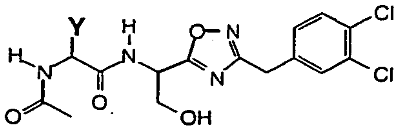


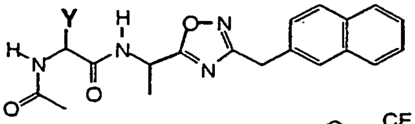
Returning to the subject of oxadiazoles, one set of illustrative compounds of particular interest include those of the following sorts of structures:

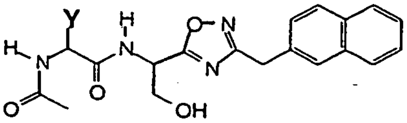


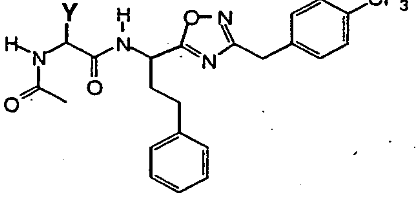


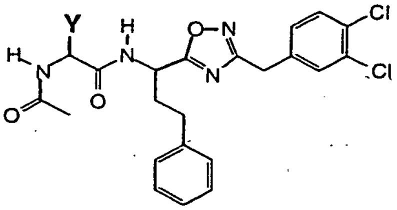






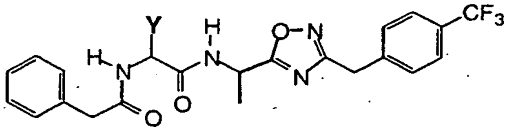


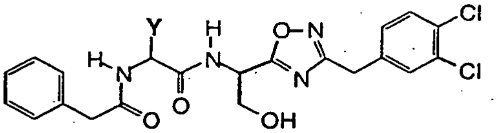


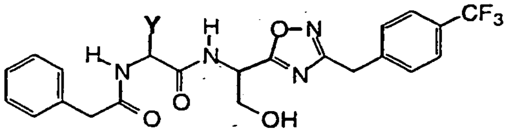


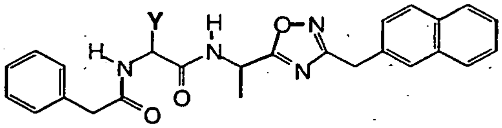
Such oxadiazoles may be useful as inhibitors of cellular signaling mediated by ZAP-70 or ZAP-70 family kinases, and thus may be useful in treating or preventing an inflammatory response in patients in need thereof. Such compounds may be used for example as immunosuppressants in patients who are going to receive, or have received, an organ or tissue transplant or in patients suffering an autoimmune disorder.

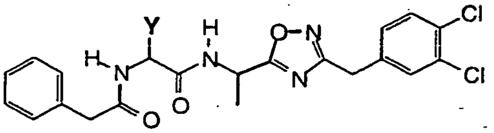
Another set of illustrative oxadiazoles of particular interest include the following types of compounds:

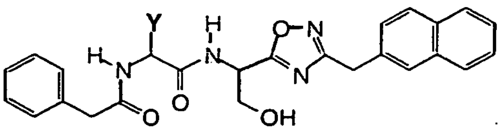




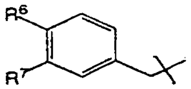




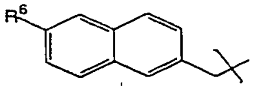




Compounds of this invention of particular interest, including the various thiazoles and oxadiazoles discussed above, include, among others, embodiments of the type in which **Y** comprises:



or



where $\mathbf{R}^6$ comprises $-PO_3RR'$, $-OPO_3RR'$, $-OSO_2NRR'$, $-(CH_2)PO_3RR'$, $-(CF_2)PO_3RR'$ or –**CRJK**; and $\mathbf{R}^7$ comprises **R** (including among others, H, alkyl, alkenyl, etc.) –CN, amido, acylamino, **J** (e.g. $-CO_2R$), or –CHO. For example, in some cases, $\mathbf{R}^6$ comprises $-OPO_3RR'$ or $-(CF_2)PO_3RR'$ and $\mathbf{R}^7$ is H. In some embodiments one or more R groups (including R', R", etc) of $\mathbf{R}^6$ comprises $-(M)_m-CH_2\mathbf{Z}$, $-(M)_m-CHZ_2$, $-(M)_m-CZ_3$, $-R^{15}$, $-M-O-CO-OR^{15}$ or $-M-O-CO-R^{15}$, where Z is H or halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic. For example, in individual cases, R^{15} is methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl, and M is CH_2, CHR (e.g. $CHCH_3$ etc.) and the like.

Compounds of this invention which are of special interest include those which bind to a given SH2 domain (or protein containing such SH2 domain) with a IC_{50} value of less than 50 µM, preferably less than 20 µM, as determined by any scientifically valid method, in vitro or in vivo. SH2 domains of current interest include those of a Src, Fyn, Lck, Yes, Blk, Lyn, Fgr, Hck, Yrk, ZAP-70, Syk, STAT or Abl protein.

Also of interest are pharmaceutical compositions comprising a compound of this invention, or a pharmaceutically acceptable derivative thereof, and one or more pharmaceutically acceptable excipients.

Compounds of this invention (or a composition containing such a compound) can be administered to cells or to animals, preferably a mammal in need thereof, as a method for inhibiting SH2–mediated signal transduction therein. In particular cases, it will be advantageous to carry out that method using a pharmaceutical composition containing a compound which specifically binds to an SH2 domain of Src, ZAP–70, Syk, or STAT 6. In other cases it will be advantageous to carry out that method where the SH2–mediated signal transduction is mediated by a PDGF receptor protein, EGF receptor protein, HER2/Neu receptor protein, fibroblast growth factor receptor protein, focal adhesion kinase protein, p130 protein, or p68 protein.

Cases in which a mammal may be in need of inhibition of SH2-mediated signaling include cases in which the mammal has a proliferative disease, cancer, restenosis, osteoporosis, inflammation, allergies, or cardiovascular disease. In such cases, administering a therapeutically effective amount of the composition to the mammal, preferably to a human patient, will constitute treating or preventing the proliferative disease, cancer, restenosis, osteoporosis, inflammation, allergic reaction, or cardiovascular disease in the recipient or a method for causing immunosuppression in the recipient.

Generally preferred compounds of this invention include any of the foregoing compounds which yield an observable IC_{50} value, when tested against an SH2 domain of interest and a pTyr-containing peptide ligand (or mimic thereof) for that SH2 domain, of 50 µM or better, preferably 5 µM or better, more preferably 1 µM or better, and even more preferably, 500 nM or better, as determined by any scientifically valid measure, especially when the SH2 domain is from a Src, Fyn, Lck, Yes, Blk, Lyn, Fgr, Hck, Yrk, ZAP, Syk, STAT or Abl protein.

A pharmaceutical composition may be prepared containing a compound of this invention (including a pharmaceutically acceptable derivative thereof) together with one or more pharmaceutically acceptable excipients.

A compound of this invention, preferably in the form of a pharmaceutical composition, may be administered to a mammal in need thereof, preferably a human patient, as a method for inhibiting SH2-mediated signal transduction in the recipient mammal. In some cases, the compound may be selected based on its ability to specifically bind to an SH2 domain, e.g. of Src, ZAP-70, Syk, or STAT 6, etc., or on its ability to inhibit a signal transduction pathway mediated by an SH2 domain-containing protein. Such use of an appropriately selected compound of this invention thus provides a method for inhibiting SH2-mediated signal transduction which is mediated by a PDGF receptor protein, EGF receptor protein, HER2/Neu receptor protein, fibroblast growth factor receptor protein, focal adhesion kinase protein, p130 protein, or p68 protein. Use of a compound of this invention may be particularly advantageous in cases in which the mammal has a proliferative disease, cancer, restenosis, osteoporosis, inflammation, allergies, or cardiovascular disease. In such cases, administering to the patient a therapeutically effective amount of a compound of this invention, preferably in the form of a pharmaceutical composition, provides a method for treating or preventing a proliferative disease, cancer, restenosis, osteoporosis, inflammation, allergies, or cardiovascular disease in the patient.

Detailed Description of the Invention

Compounds and Definitions

As mentioned above, this invention provides a novel class of compounds useful as inhibitors of signal transduction pathways mediated by the interaction of protein receptors for phosphotyrosine-containing proteins, such as proteins containing one or more SH2 domains, with their phosphotyrosine-containing ligands. Compounds of this invention comprise those of Formula I, set forth above, and are illustrated in part by the various classes, subgenera and subsets of compounds noted above, and by the various subgenera and species disclosed elsewhere herein. The compound may be in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers.

Also included are pharmaceutically acceptable derivatives of the foregoing compounds, where the phrase "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite or residue thereof, preferably one which is a signal transduction inhibitor. Pharmaceutically acceptable derivatives thus include among others pro-drugs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety which is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester which is cleaved *in vivo* to yield a compound of interest. Pro-drugs of a variety of compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention.

The term "aliphatic" as used herein includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. Unless otherwise specified, alkyl, other aliphatic, alkoxy and acyl groups preferably contain 1-8, and in many cases 1-6, contiguous aliphatic carbon atoms. Illustrative aliphatic groups thus include, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH_2-cyclopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH_2-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH_2-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl,-CH_2-cyclohexyl moieties and the like, which again, may bear one or more substituents.

Some examples of substituents of aliphatic (and other) moieties of compounds of this invention include: R, -OH, -OR, -SH, -SR,-CHO, =O, –COR, -COOH (or amide, ester, carbamate, urea, oxime or carbonate thereof), -NH_2 (or substituted amine, amide, urea, carbamate or guanidino derivative therof), halo, trihaloalkyl, cyano, -SO_2-CF_3,-OSO_2F, -$OS(O)_2R$, -SO_2-NHR, -$NHSO_2R$, sulfate, sulfonate, aryl and heteroaryl moieties. Aliphatic, heteroaliphatic, aryl and heterocyclic substituents may themselves be substituted or unsubstituted (*e.g.* mono-, di- and tri-alkoxyphenyl; methylenedioxyphenyl or ethylenedioxyphenyl; halophenyl; or -phenyl-$C(Me)_2$-CH_2-O-CO-[C3-C6] alkyl or alkylamino). Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples which follow.

The term “aliphatic” is thus intended to include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties.

As used herein, the term "alkyl" includes both straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl" and the like. Furthermore, as used herein, the language "alkyl", "alkenyl", "alkynyl" and the like encompasses both substituted and unsubstituted groups.

The term "alkyl" refers to groups usually having one to eight, preferably one to six carbon atoms. For example, "alkyl" may refer to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl tert-pentyl, cyclopentyl, hexyl, isohexyl, cyclohexyl, and the like. Suitable substituted alkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl, substituted benzyl and the like.

The term "alkenyl" refers to groups usually having two to eight, preferably two to six carbon atoms. For example, "alkenyl" may refer to prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, hex-5-enyl, 2,3-dimethylbut-2-enyl, and the like. The language "alkynyl," which also refers to groups having two to eight, preferably two to six carbons, includes, but is not limited to, prop-2-ynyl, but-2-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl, hex-5-ynyl, and the like.

The term "cycloalkyl" as used herein refers specifically to groups having three to seven. preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of other aliphatic or heteroaliphatic or heterocyclic moieties, may optionally be substituted.

The term "heteroaliphatic" as used herein refers to aliphatic moieties which contain one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched or cyclic and include heterocycles such as morpholino, pyrrolidinyl, *etc.*

The term "heterocycle" as used herein refers to cyclic heteroaliphatic and heteroaryl groups and preferably three to ten ring atoms total, includes, but is not limited to heteroaliphatic moieties such as oxetane, tetrahydrofuranyl, tetrahydropyranyl, aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine and the like, and heteroaryl moieties as described below.

The terms "aryl" and "heteroaryl" as used herein refer to stable mono- or polycyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated moieties having 3 - 14 carbon atom which may be substituted or unsubstituted. Substituents include any of the previously mentioned substituents. Non-limiting examples of useful aryl ring groups include phenyl, halophenyl, alkoxyphenyl, dialkoxyphenyl, trialkoxyphenyl, alkylenedioxyphenyl, naphthyl, phenanthryl, anthryl, phenanthro and the like. Examples of typical heteroaryl rings include 5-membered monocyclic ring groups such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, oxadiazolyl and the like; 6-membered monocyclic groups such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like; and polycyclic heterocyclic ring groups such as benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, benzothiazole, benzimidazole, tetrahydroquinoline cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, phenoxazinyl, and the like(see *e.g.* Katritzky, Handbook of Heterocyclic Chemistry). The aryl or heteroaryl moieties may be substituted with one to five members selected from the group consisting of hydroxy, C1-C8 alkoxy, C1-C8 branched or straight-chain alkyl, acyloxy, carbamoyl, amino, N-acylamino, nitro, halo, trihalomethyl, cyano, and carboxyl. Aryl moieties thus include, *e.g.* phenyl; substituted phenyl bearing one or more substituents selected from groups including: halo such as chloro or fluoro, hydroxy, C1-C6 alkyl, acyl, acyloxy, C1-C6 alkoxy (such as methoxy or ethoxy, including among others dialkoxyphenyl moieties such as 2,3-, 2,4-, 2,5-, 3,4- or 3,5-dimethoxy or diethoxy phenyl or such as methylenedioxyphenyl, or 3-methoxy-5-ethoxyphenyl; or trisubstituted phenyl, such as trialkoxy (*e.g.*, 3,4,5-trimethoxy or ethoxyphenyl), 3,5-dimethoxy-4-chloro-phenyl, *etc.*), amino, $-SO_2NH_2$, $-SO_2NH(\text{aliphatic})$, $-SO_2N(\text{aliphatic})_2$, -O-aliphatic-COOH, and -O-aliphatic-NH_2 (which may contain one or two N-aliphatic or N-acyl substituents).

A "halo" substituent may be fluoro, chloro, bromo or iodo.

With respect to nomenclature, note that asymmetric moieties such as "–G–M–" are written in the direction or order in which they are intended to be read into a given structure. Thus, "–G–M–" is distinct from "–M–G–". For example, in "Ar–A–COOR", where A is –G–M–, the structure Ar–G–M–COOR, not Ar–M–G–COOR, is intended.

Synthesis

Those of ordinary skill in this art will appreciate that compounds of this invention may be produced using any of a variety of synthetic strategies. We typically use a convergent synthetic scheme in which an intermediate comprising the desired **"YXU"** moiety, protected as appropriate, is condensed with a second intermediate comprising the desired amino moiety $\mathbf{HR^{14}N(CR^1R^2)_mB}$, again, protected as appropriate, to yield (following any necessary deprotection steps) the desired compound of Formula I. A variety of methods and materials for effecting the relevant chemical transformations, product recovery, purification and formulation are known in the art which may be adapted to use in the practice of this invention. The detailed examples which follow illustrate such syntheses and should provide helpful guidance to the practitioner.

Assays for Comparative Functional Evaluation of Compounds

Compounds of this invention may be evaluated in a variety of assays to determine their relative ability to bind to a receptor for a pTyr-containing ligand, such as a protein containing one or more SH2 or PI domains, or to otherwise inhibit an intermolecular interaction mediated by such a domain. See e.g. US 5667980 (Pawson; competitive binding assays), PCT/US97/02635 (Rickles et al; cell-based assays) and PCT/US97/06746 (Lynch et al, FP assays). Compounds may also be evaluated for their selectivity of binding to one such receptor (or family of receptors) relative to another such receptor (or family of receptors). The compounds of this invention can be further evaluated by conventional methods for possible therapeutic applications, including evaluations of toxicological and pharmacological activity. For example, the compounds may further be evaluated for activity in inhibiting cellular or other biological events mediated by a pathway involving the molecular interaction of interest using a suitable cell-based assay or an animal model. Cell-based assays and animal models suitable for evaluating inhibitory activity of a test compound with respect to a wide variety of cellular and other biological events are known in the art. New assays and models are regularly developed and reported in the scientific literature.

By way of non-limiting example, compounds which bind to an SH2 domain involved in the transduction of a signal leading to asthma or allergic episodes may be evaluated in a mast cell or basophil degranulation assay. The inhibitory activity of a test compound identified as an SH2 inhibitor by the method of this invention with respect to cellular release of specific mediators such as histamine, leukotrienes, hormonal mediators and/or cytokines, as well as its biological activity with respect to the levels of phosphatidylinositol hydrolysis or tyrosine phosphorylation can be characterized with conventional in vitro assays as an indication of biological activity. [See, e.g., Edward L. Barsumian et al, Eur. J. Immunol., 11:317-323 (1981); M. J. Forrest, Biochem. Pharmacol., 42:1221-1228 (1991) (measuring N-acetyl-betaglucosamin-adase from activated neutrophils); and Stephan et al., J. Biol. Chem., 267:5434-5441 (1992)].

For example, histamine release can be measured by a radioimmunoassay using a kit available from AMAC Inc. (Westbrook, ME). One can thus evaluate the biological activity of compounds of this invention and compare them to one another and to known active compounds or clinically relevant compounds which can be used as positive controls.

Generally speaking, in such assays IC50 scores of 20 µM or less are considered of special interest, scores below 1 µM are considered of particular interest and scores below about 500 nM are of high interest. Inhibitors of this invention may also be tested in an ex vivo assay, e.g., for their ability to block antigen-stimulated contraction of sensitized guinea pig tracheal strip tissue. Activity in this assay has been shown to be useful in predicting the efficacy of potential anti-asthma drugs.

Numerous animal models of asthma have been developed and can be used [for reviews, see Larson, "Experimental Models of Reversible Airway Obstruction". in THE LUNG, Scientific Foundations, Crystal, West et al. (eds.), Raven Press, New York, pp. 953-965 (1991); Warner et al., Am. Rev. Respir. Dis., 141:253-257 (1990)]. Species used in animal models of asthma include mice, rats, guinea pigs, rabbits, dogs, sheep and primates. Other in vivo models available are described in Cross et al., Lab Invest., 63:162-170 (1990); and Koh, et al., Science, 256:1210-1213 (1992).

By way of further example, compounds which bind to an SH2 or other domain of interest involved in the transduction of a signal involved in the initiation, maintenance or spread of cancerous growth may be evaluated in relevant conventional in vitro and in vivo assays. See e.g., Ishii et al., J. Antibiot., XLII:1877-1878 (1989); and US Patent 5,206,249 (issued 27 April 1993).

Compounds which bind to a ZAP SH2 domain or which otherwise inhibit ZAP-70-mediated signaling may be evaluated for immunosuppressive activity, e.g., in any of the well-known in vitro or in vivo immunosuppression assays.

Compounds which bind to a Src SH2 domain or which otherwise inhibit Src-mediated signaling may be evaluated for activity in a variety of assays considered predictive of activity in treating or preventing osteoporosis. Such assays include the various pit assays and calvaria assays, among others. Illustrative assays are described below.

MURINE CALVARIA ASSAY

In osteoporosis, excessive bone resorption results in decreased bone density. *In vivo* and *in vitro* models of bone resorption are used to study the processes leading to osteoporosis. *In vitro*, fetal rat long bone and murine calvaria cultures are routinely used. Both models display similar responses to parathyroid hormone (PTH), a physiological modulator of bone resorption (Stern, P.H. and N.S. Krieger. Comparison of fetal rat limb bones and neonatal mouse calvaria: effects of parathyroid hormone and 1,25-dihydroxyvitamin D_3. Calcif. Tissue Int. 35: 172-176, 1983). The calvaria model of bone resorption can be successfully used to screen osteotropic compounds as has been previously shown (Green, J.R., K. Muller and K. Jaeggi. Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. J. Bone Miner. Res. 9: 745-751, 1994.).

In one modification of the conventional calvaria model, calvaria are not labeled with $^{45}Ca^{++}$. Instead, calvarial calcium release into the media is assessed using a microtiter colorimetric calcium assay. This modification can yield more consistent responses than the radioactive methodology and provides results which are comparable to literature values for $^{45}Ca^{++}$ assays.

One calvaria culture model tests the ability of anti-resorptive compounds to prevent resorption (prophylactic model). A second model tests the ability of these compounds to terminate ongoing resorption (therapeutic model). Cytotoxicity may be assessed in both models using a lactate dehydrogenase (LDH) assay. These *in vitro* models of bone resorption may be used for routine screening and evaluation of compounds for their ability to alter osteoclast-mediated bone resorption.

Media preparation

Calcium free Dulbecco's Modified Eagle's Medium (DMEM) may be obtained in a 5x solution (Specialty Media, D-012). A 1x solution is prepared using ultrafiltered water. A suitable media contains 15% heat inactivated horse serum (Sigma, H 1270). Calcium concentration is adjusted to 1.65 to 1.83 mM using 0.2 M $CaCl_2$. Penicillin (100 U/ml) and streptomycin (0.1 mg/ml) are added to the final media preparation. Indomethacin is prepared to 0.5 mg/ml (1.397 x 10^{-7} M) in ethanol, and is added to an aliquot of DMEM to produce a final concentration of 0.5 µM. Bovine parathyroid hormone (1-34) may be obtained from Bachem (PCAL 100). PTH is solubilized in 0.1% BSA and is then diluted in DMEM to produce a final concentration of 10^{-6} M PTH. Ten-fold serial dilutions are performed down to 10^{-11} M.

Calvaria dissection

Pregnant CD-1 mice may be obtained from Charles River and are subjected to parturition. Neonatal mice (4-6 days) are cleansed with betadine and then euthanized by decapitation. Adherent skin is cleared away from the skull, exposing the calvaria. The calvaria are dissected away from the skull using a 12B scalpel. Calvaria are immediately placed into a glass petri dish containing room temperature Tyrode's Salt Solution (Sigma, T-2397). The calvaria are trimmed free of cartilage and bisected with a scalpel along the sagital suture. After dissection of all calvaria, calvaria are transferred into 24 well plates containing 0.5 µM indomethacin (Sigma, I-7378).

Culture conditions

Calvaria are incubated in 1.5 ml DMEM in 24 well tissue culture plates at 37•C, 5% CO_2/air. Plates are rocked in the incubator using a Bellco rocker platform. Calvaria are pre-incubated in 0.5 µM indomethacin for 24 hours. For each experiment, 6 to 8 random calvaria halves are used for each group. Both halves from a single mouse are never in the same group. Experiments are repeated at least three times.

Prophylactic calvaria experiment

After the 24h pre-incubation period, calvaria are thoroughly washed in indomethacin-free DMEM. Calvaria are then transferred to new wells containing various PTH concentrations, and are cultured for an additional 72 hours. Media samples (30 µl) are obtained every 24 hours and assayed for calcium and LDH activity.

Therapeutic calvaria experiment

At the end of the 24h pre-incubation period, the calvaria are washed free of indomethacin using DMEM. Calvaria are then transferred to new wells containing DMEM or various concentrations of PTH. After 24 hours calvaria are transferred into new wells with fresh media (PTH or DMEM) and cultured an additional 48 hours before addition of control vehicle. This may be accomplished by adding 3 µl of DMSO to new wells, and transferring each calvaria along with its media into wells. Culture continues for a further 24 hours. Media samples are obtained after 72 hours and 96 hours in culture with PTH and assayed for calcium. Additional samples are obtained after 48, 72, and 96 hours in culture with PTH and assayed for LDH.

Calcium Assay

A commercially available diagnostic calcium assay (Sigma, No. 588-3), modified for use in a microtiter format, may be used to determine circulating serum calcium concentrations. This colorimetric assay is dependent on the specific, high affinity complexation of calcium with arsenazo III dye under acidic conditions, which occurs with 1:1 stoichiometry and absorbs at 600 nm (Bauer, P.J. Affinity and stoichiometry of calcium binding by Arsenazo III. Anal Biochem, 110:61, 1981; Michaylova, V and P Ilkova. Photometric determination of micro amounts of calcium with Arsenazo III. Anal Chim Acta, 53: 194, 1971). Magnesium has very low affinity for arsenazo III.

Briefly, 15 µl of media or rat sera (see below) is diluted 18-fold with ultrafiltered water (nearly calcium-free). Fifty µl of this solution are pipetted into microtiter wells (Nunc, Maxisorp, flat-bottom, 0.4 ml/well). Standards of 0, 0.5, 1, 2.5, 3.75, 5, 6.25, and 7.5 mg/dl (mg%) calcium, diluted 8-fold with ultrafiltered water from control standards (Sigma, 360-11), are used to construct standard curves.. Once all standards and samples are pipetted onto the plate, 150 µl of diagnostic reagent is added to initiate complexation. Optical density measurements are obtained on a microtiter plate reader (Molecular Devices, ThermoMax) at 600 nm.

Lactate dehydrogenase assay

Phosphate buffer is prepared in distilled water (0.26 M $K_2HPO_4 \cdot 3H_2O$, 0.26 M KH_2PO_4; pH 7.4). A mix consisting of: 22 ml of phosphate buffer, 6 ml distilled water and 2.0 ml of 0.01 M pyruvate is prepared. NADH is prepared to 0.4 mg/ml in phosphate buffer.

Ten µl of media samples obtained from incubated calvaria are added to 96 well plates. Wells containing 10 µl of DMEM serve as blanks. To each well, 90 µl distilled water and 150 µl phosphate mix is added. 50 µl NADH is added using an eight channel pipette immediately before the plate is read on a microtiter plate reader at 340 nm. A kinetic assay is performed for 10 minutes, with a read interval of 20 seconds.

THYROID/PARATHYROIDECTOMIZED RAT MODEL of BONE RESORPTION

Parathyroid hormone (PTH) replacement in thyroparathyroidectomized (TPTX) rats is routinely used as an *in vivo* model of controlled bone resorption. Rats are the species of choice since the mechanisms of bone modeling in the rat resemble those in humans. In addition, hormones and pharmacologic agents have similar effects on both rat and human bone (Frost, H.M. and W.S.S. Jee. On the rat model of human osteopenias and osteoporoses. Bone and Mineral, 18: 227-236, 1992). Removal of the thyroid and parathyroid glands results in a rapid loss of parathyroid hormone (PTH) from the circulation. Since PTH induces osteoclast-mediated bone resorption, this process is inhibited in TPTX animals. In addition, PTH mediates calcium reabsorption from the kidneys and absorption from the small intestines. The lack of these activities work in concert to decrease serum calcium levels. In the absence of PTH, rats remain in a hypocalcemic state. Restriction of dietary calcium limits intestinal calcium absorption and renal calcium filtration such that serum calcium levels are primarily influenced by bone resorption. Controlled PTH replacement therapy results in a controlled return of serum calcium to baseline levels. When replacement occurs, concomitantly with a low calcium diet, serum calcium increase is due to PTH-induced osteoclast-mediated bone resorption. In this model, drugs which inhibit bone resorption prevent the PTH-mediated return of serum calcium to baseline levels.

Female Wistar rats (226-250 gm, Charles River) are fasted overnight and anesthetized with 0.15 ml of 1.2% tribromoethanol (TBE). The ventral neck area is shaved and swabbed with betadine and isopropanol. A midline incision is made in the neck through the skin and superficial muscle layer, as well as in the sternohyoid muscle. Blunt dissection is performed to expose the thyroid gland. The thyroid gland is carefully isolated from the trachea, thyrohyoid muscle, as well as adjacent nerves and blood vessels, using blunt dissection. The thyroid gland is excised one lobe at a time. Cautery is performed for hemostasis. Care is taken to avoid damaging the recurrent laryngeal nerve since damage to it is shown to affect serum calcium concentrations (Hirsch, P.F., G.F. Gauthier and P.L. Munson. Thyroid hypocalcemic principle and recurrent laryngeal nerve injury as factors affecting the response to parathyroidectomy in rats. Endocrinology, 73: 244-252, 1963. *et al.*, 1963). The incisions are closed using 3-0 vicryl. The wound is coated with triple antibiotic ointment (Fougera; 400 units/g bacitracin zinc, 5 mg/g neomycin sulfate, 5000 units/g polymyxin B sulfate). Following TPTX, rats are pair fed a low calcium diet (Harlan Teklad TD 95065; $\leq 0.003\%$ Ca^{++}, $\leq 0.04\%$ PO_4) such that each rat receives the same quantity of food. Rats are fed at least 5 grams, but not more than 10 grams. of food. Rats consuming less than 3.0 grams of food receive the nutritional supplement Nutri-Cal p.o. (Evsco; ≤0.0033% calcium).

PTH Dose Response/Pump implantation

Three days post TPTX, rats which are found to be hypocalcemic, based on day 2 serum calcium levels, are implanted with PTH-containing Alzet mini-osmotic pumps (ALZA, model 2001D) which pumps at a rate of 1 μl/h. The rats are anesthetized with ketamine (50 mg/kg, i.p.) and acepromazine (1.67 mg/kg, i.p.). The scapula region is shaved and prepared for surgery with betadine and isopropanol. A lateral incision of approximately 2 cm in length is made between the scapulae. Using hemostats, a subcutaneous pocket is created into which the Alzet pump is inserted. The wound is closed either with nylon suture or with staples. Triple antibiotic ointment is applied as described previously.

Bovine parathyroid hormone 1-34 (PTH) (Bachem California, PCAL100) is prepared in vehicle (10^{-3} N HCl, 0.15 M NaCl, 20 mg/ml cysteine·HCl) at the following concentrations: 0.156, 0.47, 1.56, 4.7, 15.6, and 156 μM. Alzet mini-osmotic pumps are filled with the PTH solution and maintained in 37•C saline for 4 hours prior to implantation.

Serum Samples

Rats are anesthetized by CO_2 from dry ice and daily blood samples are obtained via cardiac puncture using a 27 gauge needle. Baseline samples are taken just prior to TPTX. Daily samples are obtained in the morning. Samples are allowed to clot on their side for several hours and subsequently spun at 1000xg for 15 minutes to obtain serum. Serum is aliquoted and stored in the refrigerator until assayed for serum calcium. Serum calcium is measured (see above) daily for at least 7 days following TPTX.

Uses of Compounds of This Invention

Compounds of this invention which bind to an SH2 domain of interest may be used as biological reagents in assays as described herein for functional classification of a pTyr-binding domain (e.g. SH2 or PI domain) of a particular protein, particularly a newly discovered protein. Families or classes of such proteins which bind to pTyr-containing ligands may now be defined functionally, with respect to ligand specificity. Moreover, compounds of this invention can be used to inhibit the occurrence of biological events resulting from molecular interactions mediated by the protein of interest. Inhibiting such interactions can be useful in research aimed at better understanding the biology of events mediated by the binding of pTyr-containing ligands to their receptors.

Such compounds would be useful, for example, in the diagnosis, prevention or treatment of conditions or diseases resulting from a cellular processes mediated by the binding of a pTyr-containing ligand with a receptor therefor. For example, a patient can be treated to prevent the occurrence or progression of osteoporosis or to reverse its course by administering to the patient in need thereof an SH2inhibitor which selectively binds Src SH2 or otherwise interferes with Src-mediated signaling.

There are many other conditions for which such signal transduction inhibitors may be useful therapeutically, including, e.g., breast cancer where the SH2 domain-containing proteins Src, PLCgamma and Grb7 have been implicated. Other relevant conditions include prostate cancer, in which case targeting Grb2, PLCgamma, and PI3K, all of which contain SH2 domains, may be useful in treatment or prevention of the disease. Inhibition of the interaction of Grb2 or Abl SH2 domains with BCR-abl may be useful to treat chronic myelogenous leukemia (CML) or acute myelogenous leukemia (AML).

Still other relevant applications include the prevention of interferon-, growth factor-, or cytokine-mediated diseases (e.g. inflammatory diseases) by targeting the interaction of STAT proteins with their pTyr-containing ligands or otherwise inhibiting their signal transduction pathways. Agents that block the SH2 domains of ZAP-70 or otherwise inhibit ZAP-70-mediated signaling would be candidates for the treatment of immune-related disorders such as rejection of transplanted bone marrow, skin or other organs; rheumatoid arthritis; inflammatory bowel disease; and systemic lupus erythmatosis, and a variety of autoimmune diseases.

By virtue of the capacity to inhibit protein-protein interactions or a relevant kinase or phosphatase activity required for cellular events of pharmacologic importance, compounds of this invention which inhibit cellular signal transduction may be used in pharmaceutical compositions and methods for treatment or prevention in a subject in need thereof. Such inhibitors can be used to treat or reduce the risk of the diseases or their pathological effects mediated by such interactions.

For example, drugs that completely block one of the two ZAP SH2 domains should effectively prevent ZAP from associating with the activated TCR and thus block T cell activation. A ZAP antagonist or inhibitor would specifically inhibit T cells and avoid the toxicity of the currently used immunosuppressive drugs, FK506 and cyclosporin, which target the more ubiquitously expressed protein, calcineurin. Since calcineurin is required for cellular activities in several tissues in addition to T cells, cyclosporin and FK506 cause side effects in the kidney and central nervous system which limit their application largely to patients with organ transplant rejection.

Therapeutic/Prophylactic Administration & Pharmaceutical Compositions

Compounds of this invention can exist in free form or, where appropriate, in salt form. Pharmaceutically acceptable salts of many types of compounds and their preparation are well-known to those of skill in the art. The pharmaceutically acceptable salts of compounds of this invention include the conventional non-toxic salts or the quaternary ammonium salts of such compounds which are formed, for example, from inorganic or organic acids of bases.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent.

This invention also relates to pharmaceutical compositions comprising a therapeutically (or prophylactically) effective amount of the compound, and a pharmaceutically acceptable carrier or excipient. Carriers include e.g. saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof, and are discussed in greater detail below. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc*. Formulation may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid.

Illustrative solid carrier include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions ,and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Illustrative liquid carriers include syrup, peanut oil, olive oil, water, etc. Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carders are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

The carrier or excipient may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate along or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like. When formulated for oral administration, 0.01% Tween 80 in PHOSAL PG-50 (phospholipid concentrate with 1,2-propylene glycol, A. Nattermann & Cie. GmbH) has been recognized as providing an acceptable oral formulation for other compounds, and may be adapted to formulations for various compounds of this invention.

A wide variety of pharmaceutical forms can be employed. If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampule or vial or nonaqueous liquid suspension.

To obtain a stable water soluble dosage form, a pharmaceutically acceptable salt of the compound may be dissolved in an aqueous solution of an organic or inorganic acid, such as a 0.3M solution of succinic acid or citric acid. Alternatively, acidic derivatives can be dissolved in suitable basic solutions. If a soluble salt form is not available, the compound is dissolved in a suitable cosolvent or combinations thereof. Examples of such suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin, polyoxyethylated fatty acids, fatty alcohols or glycerin hydroxy fatty acids esters and the like in concentrations ranging from 0-60% of the total volume.

Various delivery systems are known and can be used to administer the compound, or the various formulations thereof, including tablets, capsules, injectable solutions, encapsulation in liposomes, microparticles, microcapsules, *etc*. Methods of introduction include but are not limited to dermal, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, pulmonary, epidural, ocular and (as is usually preferred) oral routes. The compound may be administered by any convenient or otherwise appropriate route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*) and may be administered together with other biologically active agents. Administration can be systemic or local. For treatment or prophylaxis of nasal, bronchial or pulmonary conditions, preferred routes of administration are oral, nasal or via a bronchial aerosol or nebulizer.

In certain embodiments, it may be desirable to administer the compound locally to an area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, by injection, by means of a catheter, by means of a suppository, or by means of a skin patch or implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the side of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

Administration to an individual of an effective amount of the compound can also be accomplished topically by administering the compound(s) directly to the affected area of the skin of the individual. For this purpose, the compound is administered or applied in a composition including a pharmacologically acceptable topical carrier, such as a gel, an ointment, a lotion, or a cream, which includes, without limitation, such carriers as water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, or mineral oils.

Other topical carriers include liquid petroleum, isopropyl palmitate, polyethylene glycol, ethanol (95%), polyoxyethylene monolaurate (5%) in water, or sodium lauryl sulfate (5%) in water. Other materials such as anti-oxidants, humectants, viscosity stabilizers, and similar agents may be added as necessary. Percutaneous penetration enhancers such as Azone may also be included.

In addition, in certain instances, it is expected that the compound may be disposed within devices placed upon, in, or under the skin. Such devices include patches, implants, and injections which release the compound into the skin, by either passive or active release mechanisms.

Materials and methods for producing the various formulations are well known in the art and may be adapted for practicing the subject invention. See *e.g.* US Patent Nos. 5,182,293 and 4,837,311 (tablets, capsules and other oral formulations as well as intravenous formulations) and European Patent Application Publication Nos. 0 649 659 (published April 26, 1995; illustrative formulation for IV administration) and 0 648 494 (published April 19, 1995; illustrative formulation for oral administration).

The effective dose of the compound will typically be in the range of about 0.01 to about 50 mg/kgs, preferably about 0.1 to about 10 mg/kg of mammalian body weight, administered in single or multiple doses. Generally, the compound may be administered to patients in need of such treatment in a daily dose range of about 1 to about 2000 mg per patient.

The amount of compound which will be effective in the treatment or prevention of a particular disorder or condition will depend in part on the nature and severity of the disorder or condition, which can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. The precise dosage level should be determined by the attending physician or other health care provider and will depend upon well known factors, including route of administration, and the age, body weight, sex and general health of the individual; the nature, severity and clinical stage of the disease; the use (or not) of concomitant therapies.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

* * * * *

The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should also be appreciated that those cited references are incorporated herein by reference to help illustrate the state of the art.

In addition, the full contents of US Patent Applications USSN 09/190,424 (Weigele et al, "Novel Signal Transduction Inhibitors, Compositions Containing Them & Uses Thereof", filed November 12, 1998), and USSN 60/108,106 (Shakespeare et al, "Bicyclic Signal Transduction Inhibitors, Compositions Containing Them & Uses Thereof", filed November 12, 1998) are incorporated by reference herein. Those documents provide additional synthetic and other guidance which may be of interest to the practitioner of the subject invention.

The following examples contain important additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

Examples

General: Compounds of this invention can be prepared by convergent synthesis as illustrated in the following examples. Typically, a carboxylic acid, e.g., Ac-Tyr(PO_3Bn_2)-OH or Boc-Tyr(PO_3Bn_2)-OH, for example, is coupled with a heterocyclic amine using standard materials and methods for peptide coupling, including any necessary or desired protection and subsequent deprotection.

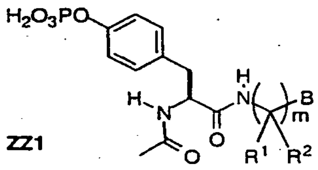
Abbreviations. The following abbreviations are used in this document.

Abu	alpha-aminobutyric acid
Ac	acetyl
aq	aqueous
Bn	benzyl
Boc	tertiary butyloxycarbonyl
BOC-ON	$(CH_3)_3COCO_2N=C(C_6H_5)CN$
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
Chx	cyclohexyl
DCM	dichloromethane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
DIBAL-H	diisobutylaluminum hydride
DIEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide or methyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Gln	glutamine
Glu	glutamic acid
Gly	glycine
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOBT	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
imid	imidazole
Lawesson's Reagent	[2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]
LiHMDS	lithium hexamethyldisilazide or lithium bis(trimethylsilyl) amide
MeCN	acetonitrile
MS	mass spectrometry
Ms	methanesulfonyl (mesyl)
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
Rochelle salt	potassium sodium tartrate
satd	saturated
Su	succinimide
pyr	pyridine

RT	room temperature
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	tertiarybutyldimethylsilyl
Tf	trifluoromethanesulfonyl or trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Thr	threonine
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSE	trimethylsilylethanol
Tyr	tyrosine

◆ ◆ ◆ ◆

General Methods A-G: Preparation of N-acetyl phosphate derivatives



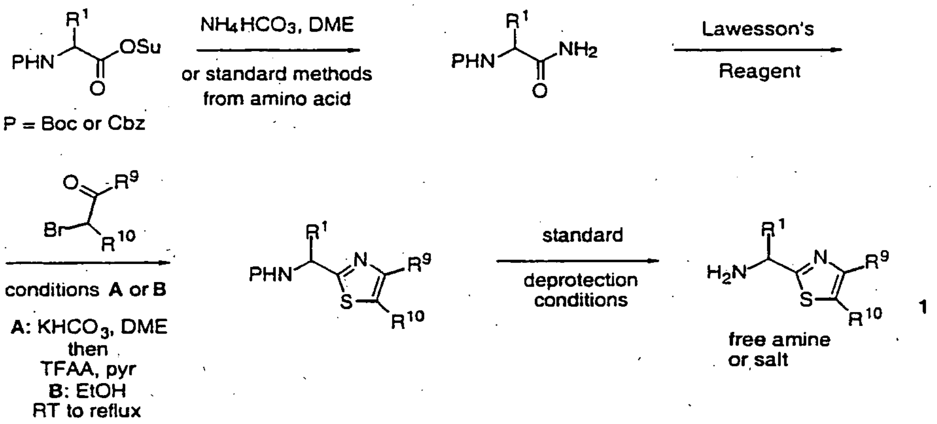
ZZ1

Compounds such as Compound ZZ1 can be prepared according to General Methods A-G, as exemplified by the following examples. General Methods C and D exemplify typical coupling strategies, which can be modified with obvious standard manipulations and as shown here in General Methods A-G as well as in the following General Methods H-ZT.

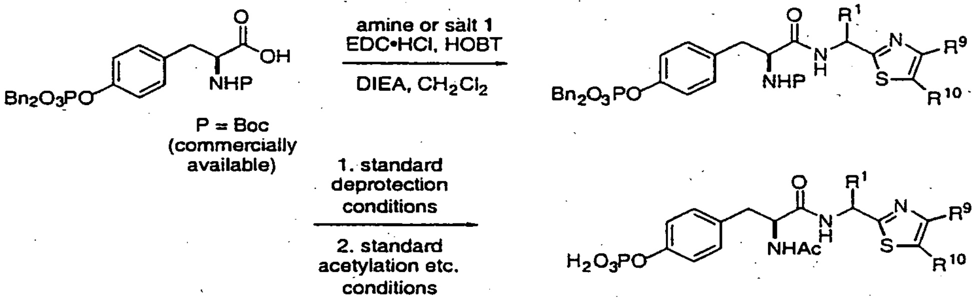
General Methods A and B: Preparation of thiazoles and oxazoles via the Hantzsch synthesis:

Many thiazoles and oxazoles can be prepared via standard Hantzsch thiazole synthesis with alpha halo ketones and thioamides or amides.

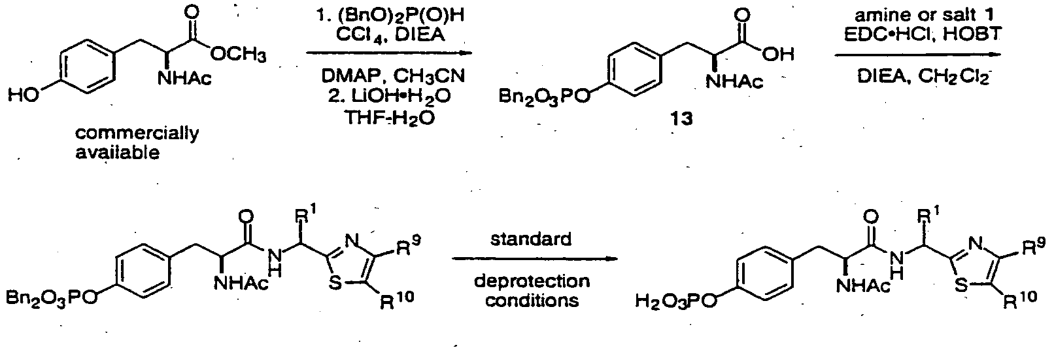
Standard thiazole formation - Conditions A and B:



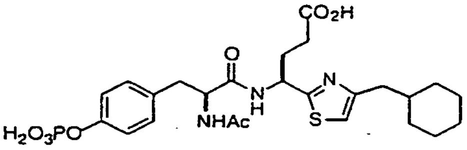
General Method C - Coupling Conditions C:


P = Boc (commercially available)
amine or salt 1
EDC•HCl, HOBT
DIEA, CH2Cl2
1. standard deprotection conditions
2. standard acetylation etc. conditions

General Method D - Coupling Conditions D:



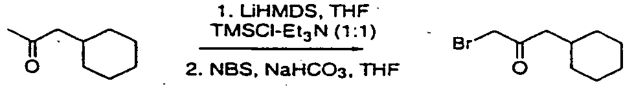
1. Compound A



A

Compounds such as Compound A can be prepared using thiazole formation Conditions A followed by Coupling Conditions C. Experimental details for the synthesis of Compound A are as follows:

Preparation of Bromomethyl Ketone 2:



2

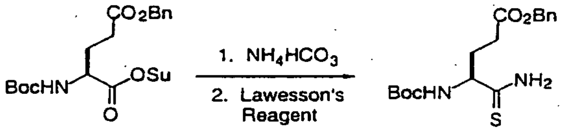
Bromomethyl ketone **2** can be prepared according to the procedure found in Hajos, Z. G.; Wachter, M. P.; Werblood, H. M.; Adams, R. E. *J. Org. Chem.* **1984**, *49*, 2600.

To a solution of 8.56 mL (8.56 mmol) of LiHMDS (1.0 M solution in THF) in 25 mL of THF at -78 °C (in a flame dried 250 mL round bottom flask) was added 1.0 g (7.13 mmol) of cyclohexylacetone in 50 mL of THF via cannula over 10 min followed by a 5 mL rinse. The resulting bright yellow solution was kept at -78 °C for 40 min whereupon 5.9 mL (21.4 mmol) of the supernatant of a 1:1 mixture of TMSCl-Et_3N (after centrifugation) was added via syringe. The resulting mixture was stirred at -78 °C for 1.5 h, quenched with 450 mg $NaHCO_3$, followed by 45 mL saturated aqueous $NaHCO_3$, allowed to warm to RT, and then diluted with Et_2O, water and brine. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The volatile crude silyl enol ether was used directly in the next step.

To a solution of the crude silyl enol ether in 40 mL THF at RT was added 719 mg (8.56 mmol) of $NaHCO_3$, and the resulting slurry was cooled to -78 °C. At this time, 1.27 g (7.13 mmol) of NBS was added in one portion, and the resulting mixture stirred at -78 °C for 30 min, warmed to RT, quenched with 450 mg $NaHCO_3$, followed by 45 mL saturated aqueous $NaHCO_3$, and then diluted with Et_2O, water and brine. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over

Na_2SO_4 and concentrated. Flash chromatography (elution with 7:1 hexanes-Et_2O) gave 1.23 g (78.8%) of a volatile pale oil: R_f 0.39 (7:1 hexanes-Et_2O).

Preparation of S-4-(benzyloxycarbonyl)-2-(tert-butoxycarbonylamino)thiobutyramide (3):



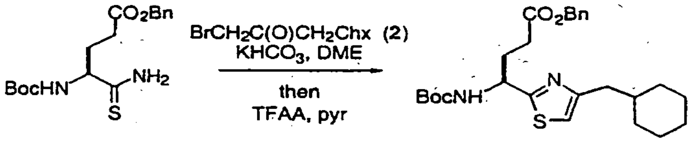
3

The intermediate amide can be prepared according to the procedure found in Nozaki, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2647.

To a mixture of 4.0 g (9.21 mmol) of Boc-Glu(OBn)-OSu in 45 mL of CH_2Cl_2 and 5 mL of dioxane at RT was added 2.2 g (27.6 mmol) of ammonium hydrogen carbonate. The resulting mixture was stirred at RT for 19 h, diluted with CH_2Cl_2 and water and stirred until clear. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude amide was used directly in the next step.

To a mixture of the crude amide in 50 mL of DME and 20 mL of THF at RT was added 2.05 g (5.07 mmol) of Lawesson's reagent. The resulting mixture was stirred at RT for 14 h and concentrated. Flash chromatography (elution with 2:1 hexanes-EtOAc) gave 3.14 g (96.6%) of a white solid: R_f 0.56 (3:1 hexanes-EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 351 (M-H).

Preparation of Thiazole 4:

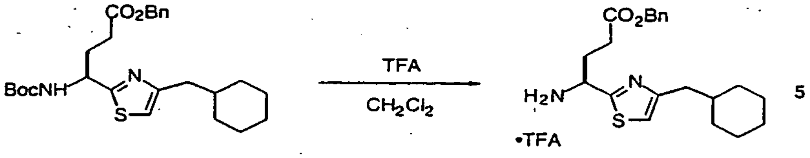


4

Thiazole **4** can be prepared according to Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473 and Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235.

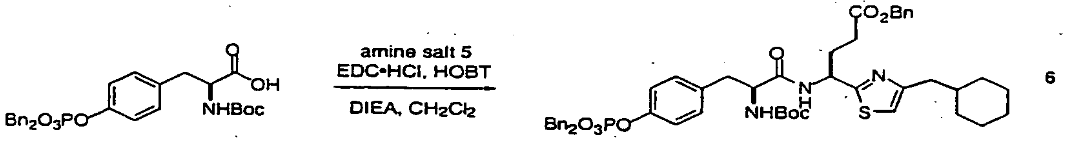
To a solution of 348 mg (0.987 mmol) of thioamide **3** in 5 mL of DME at -15 °C was added 791 mg (7.90 mmol) of $KHCO_3$. The resulting mixture was stirred at -15 °C for 5 min whereupon 516 mg (2.35 mmol) of bromide **2** in 2 mL of DME was added via syringe followed by two 0.5 mL DME rinses. The resulting mixture was stirred at -15 °C for 1 h, at RT for 2.5 h, and then recooled to -15 °C. At this point, a cooled solution of 0.558 mL (3.95 mmol) of TFAA in 0.639 mL (7.90 mmol) of pyridine was added via syringe. The resulting mixture was stirred at -15 °C for 50 min, warmed to RT, then diluted with CH_2Cl_2 and H_2O. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (elution with 2:1 hexanes-Et_2O then 1:1 hexanes-Et_2O) gave 423 mg (90.6%) of a pale oil: R_f 0.29 (1:1 hexanes-Et_2O). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 946 (M-H).

Preparation of amine **5** TFA salt:



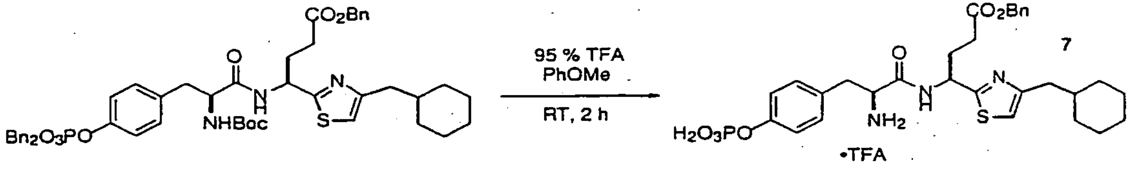
To a solution of 423 mg (0.895 mmol) of Boc-protected amine **4** in 6 mL of CH_2Cl_2 at RT was added 0.5 mL of TFA. The resulting mixture was stirred at RT for 30 min whereupon an additional 0.5 mL of TFA was added. The resulting mixture was stirred at RT for 1.75 h and concentrated *in vacuo* to give 497 mg of a white foam. The crude amine salt was used directly in the next step.

Preparation of coupling product **6**:



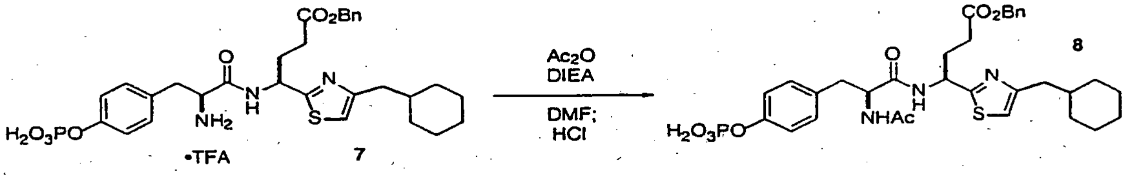
To a solution of 497 mg of crude amine salt **5** (assume 0.895 mmol), 0.648 mL (3.72 mmol) of DIEA and 403 mg (0.745 mmol) of Boc-Tyr(PO_3Bn_2)-OH in 7.5 mL of CH_2Cl_2 at RT was added 171 mg (1.12 mmol) of HOBT followed by 214 mg (1.12 mmol) of EDC•HCl. The resulting mixture was stirred at RT for 4 h, then diluted with CH_2Cl_2 and water. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (elution with 1:1 hexanes-EtOAc) gave 404 mg (60.6%) of a white foam: R_f 0.30 (1:1 hexanes-EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 897 (M+H).

Preparation of amine 7 TFA salt:



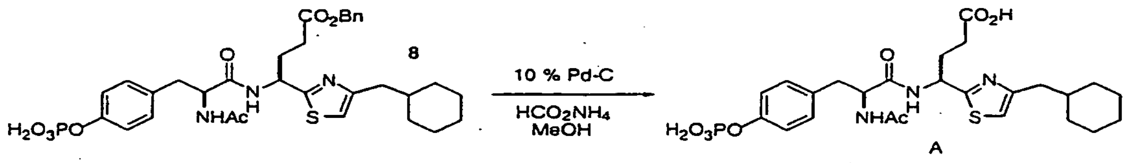
To 337 mg (0.376 mmol) of Boc-protected amine **6** and 0.5 mL of anisole was added 7.5 mL of 95% TFA (aq.). The resulting solution was stirred at RT for 2 h and concentrated to a pale gold oil. White granular crystals were formed by adding Et_2O and scraping and crushing the solid in the flask. The crystals were rinsed three times with Et_2O (supernatant removed via pipet) to give 190 mg (69% assuming TFA salt) of a granular white solid. The combined supernatants were combined with those from another batch, concentrated and crystallized as above to yield a second crop. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 616 (M-H).

Preparation of acetamide **8**:



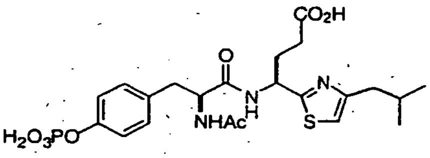
To 189 mg (0.259 mmol) of amine salt **7** in 2.5 mL of DMF at 0 °C was added via syringe 0.226 mL (1.30 mmol) of DIEA followed by 0.049 mL (0.52 mmol) of Ac_2O. The resulting solution was stirred at 0 °C for 1.25 h and then at RT for 2 h whereupon it was quenched with 1.5 mL 2 N HCl. The resulting mixture was stirred at RT for 15 min and then diluted with EtOAc. The organic layer was washed with water. The combined aqueous layers were extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. HPLC and MS indicated desired product (658 (M+H)) as well as over acetylation product (700.35 (M+H)). The residue was dissolved in 3 mL DMF, stirred with 0.5 mL 2 N HCl for 30 min, and worked up as above. White granular crystals were formed by adding Et_2O and scraping and crushing the solid in the flask. The crystals were rinsed three times with Et_2O (supernatant removed via pipet) to give 114 mg (67%) of a granular white solid. The combined supernatants were concentrated to yield 31 mg (18%) of a second crop. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 658 (M-H).

Preparation of Compound A:



To a slurry of 114 mg (0.173 mmol) of benzyl ester 8 in 2.5 mL of MeOH at RT was added 55 mg (0.867 mmol) of NH_4CO_2H followed by 100 mg of 10% Pd-C. The resulting mixture was heated at 67 °C for 35 min, cooled to RT, filtered through Celite and the filtrate concentrated. The resulting concentrate was dissolved in H_2O and lyophilized (repeated several times) until the mass remained constant, yielding 105 mg of a fluffy white solid. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 568 (M+H).

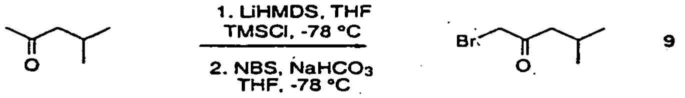
2. Compound B



B

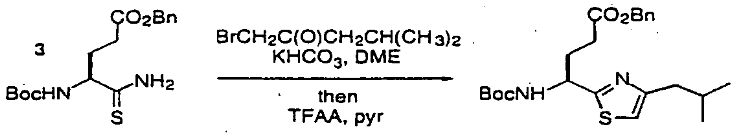
Compounds such as Compound B can be prepared using thiazole formation Conditions A followed by Coupling Conditions D. Experimental details for the synthesis of compound B are as follows:

Preparation of Bromomethyl Ketone 9:



Bromoketone 9 was prepared as bromoketone 2 except that TMSCl was used rather than the centrifugate from 1:1 Et_3N-TMSCl. Flash chromatography (elution with 6:1 hexanes-Et_2O) gave 1.8 g (50.2%) of a very volatile pale oil: R_f 0.38 (6:1 hexanes-Et_2O).

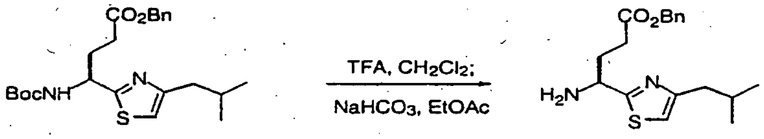
Preparation of Thiazole **10**:



10

Thiazole **10** can be prepared as shown for the preparation of thiazole **4**. Flash chromatography (elution with 3:2 hexanes-Et_2O) gave 0.95 g (80.5%) of a pale oil: R_f 0.50 (1:1 hexanes-Et_2O).

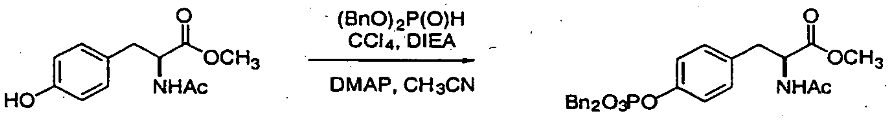
Preparation of amine **11**:



11

To a solution of 0.95 g (2.20 mmol) of Boc-protected amine **10** in 15 mL of CH_2Cl_2 at RT was added 1.5 mL of TFA. The resulting mixture was stirred at RT for 1.3 h whereupon an additional 1.5 mL of TFA was added. The resulting mixture was stirred at RT for 1.7 h and then concentrated. The resulting oil was dissolved in EtOAc and 5% aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography (elution with 12:1 CH_2Cl_2-MeOH) gave 634 mg (86.8%) of a white foam: R_f 0.46 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 333 (M+H).

Preparation of Dibenzyl phosphate **12**:



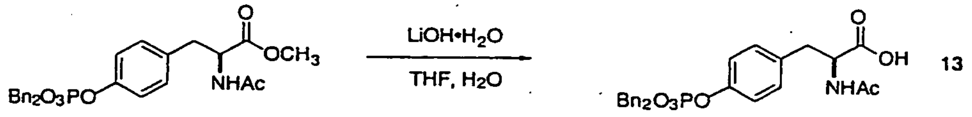
12

Dibenzyl phosphate **12** can be prepared according to the procedure found in Silverberg, L. J.; Dillon, J. L.; Vemishetti, P. *Tetrahedron Lett.* **1996**, *37*, 771.

To a mixture of 5 g (21.1 mmol) of N-acetyl-L-tyrosine methyl ester in 300 mL of CH_3CN at -10 °C was added 10.2 mL (105.5 mmol) of CCl_4. The resulting mixture was stirred at -10 °C for 5 min whereupon 8.1 mL (46.5 mmol) of DIEA, 70 mg (0.57 mmol) of DMAP and 8.29 g (31.6 mmol) of dibenzyl phosphite were added. The resulting mixture was stirred at -10 °C for 1 h and then at 0 °C for 30 min. The mixture was then quenched with

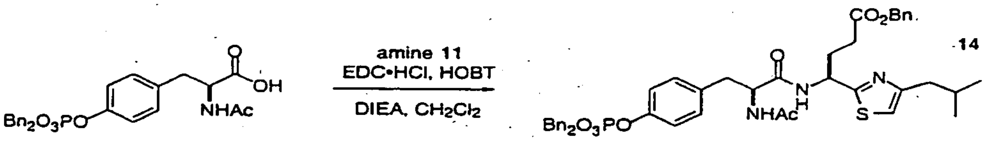
25 mL 0.5 M KH_2PO_4 and allowed to warm to RT. The quenched reaction mixture was diluted with H_2O, concentrated, then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (elution with 5% MeOH in CH_2Cl_2) gave 9.2 g (87.6%) of a pale oil: R_f 0.66 (5% MeOH in CH_2Cl_2).

Preparation of Acid **13**:



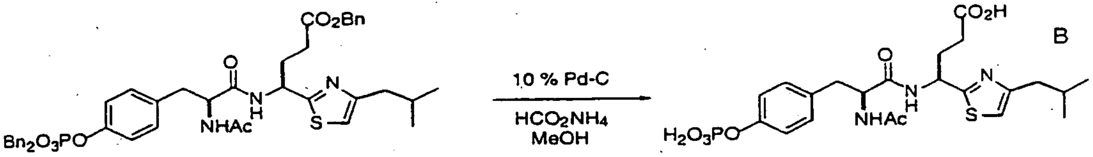
To a solution of 9.2 g (18.5 mmol) of methyl ester **12** in 150 mL of THF at 0 °C was added via addition funnel a solution of 0.855 g (20.4 mmol) of LiOH•H_2O dissolved in 100 mL of H_2O over 20 min. The resulting mixture was stirred at 0 °C for 1.5 h and concentrated. The aqueous reaction mixture was washed two times with EtOAc and acidified to pH 2-3. The acidified aqueous layer was then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated, giving 8.2 g (91.7%) of a thick oil: R_f 0.24 (5% MeOH in CH_2Cl_2). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 482 (M-H).

Preparation of coupling product **14**:



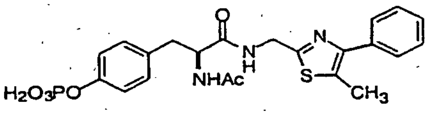
To a solution of 418 mg (0.865 mmol) of Ac-Tyr(PO_3Bn_2)-OH (**13**) and 345 mg (1.04 mmol) of amine **11** in 6 mL of CH_2Cl_2 at RT was added 0.452 mL (2.59 mmol) of DIEA followed by 159 mg (1.04 mmol) of HOBT and 199 mg (1.04 mmol) of EDC•HCl. The resulting mixture was stirred at RT for 5.75 h (TLC indicated the presence of both starting materials) whereupon an additional 20 mg each of HOBT and EDC•HCl were added. The resulting mixture was stirred at RT for 1h and concentrated (no change from previous TLC). The residue was then dissolved in EtOAc and 5% $NaHCO_3$. The organic layer was washed with H_2O and 10% citric acid, dried over Na_2SO_4 and concentrated. Flash chromatography (elution with 12:1 CH_2Cl_2 -MeOH) gave 368 mg (53.3%) of a pale oil: R_f 0.54 (9:1 CH_2Cl_2-MeOH).

Preparation of **B**:



To a mixture of 100 mg (0.125 mmol) of benzyl ester **14** in 2.5 mL MeOH at RT was added 39.5 mg (0.627 mmol) of NH_4CO_2H followed by 50 mg of 10% Pd-C. The resulting mixture was heated at 67 °C for 50 min, cooled to RT, filtered through a pad of Celite with MeOH and the resulting filtrate was concentrated. The slightly blackened oil was filtered through a pipet with a pad of Celite and a cotton plug, then through another pad of Celite, both with MeOH and a little CH_2Cl_2. The filtrate was concentrated and the residue was dissolved in H_2O and lyophilized to a glassy solid. The solid was dissolved again in H_2O and lyophilized until the mass remained constant (one more time), yielding 72.6 mg of a fluffy pale yellow solid. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 528 (M+H).

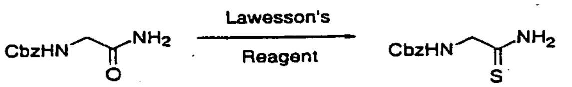
3. Compound C



C

Compounds such as Compound C can be prepared using thiazole formation Conditions B followed by Coupling Conditions D. Experimental details for the synthesis of Compound C are as follows:

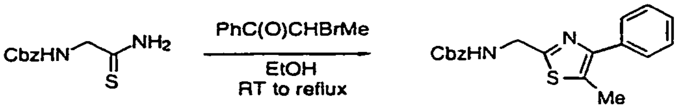
Preparation of thioamide **15**:



15

Thioamide **15** can be prepared following the procedure described for the preparation of thioamide **3** using the commercially available N-Cbz-glycinamide as the starting material. Flash chromatography (elution with 2:1 hexanes-EtOAc) provided 4.05 g (75.1%) of a white solid: R_f 0.50 (1:1 hexanes-EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 449 (M+H).

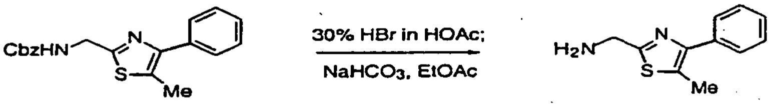
Preparation of thiazole **16**:



16

To a solution of 1.0 g (4.46 mmol) of thioamide **15** in 20 mL of EtOH at RT was added 0.882 mL (5.80 mmol) of 2-bromopropiophenone (90% tech.). The resulting mixture was stirred at RT for 2.75 h, at 78 °C for 7 h, and then cooled to RT and concentrated. Flash chromatography (elution with 2:1 hexanes-EtOAc followed by 1:1 hexanes-EtOAc, then EtOAc, then 2:1 CH_2Cl_2-MeOH) provided 0.80 g (53.0%) of a white foam [R_f 0.50 (1:1 hexanes-EtOAc)] and 0.86 g of slightly impure material which was retained for additional purification.

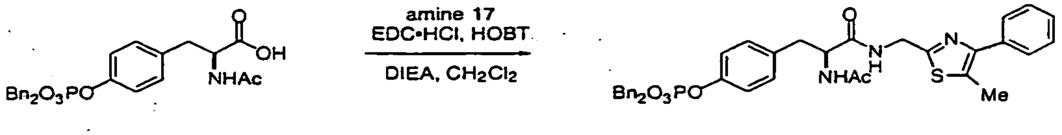
Preparation of amine **17**:



17

To 800 mg (2.36 mmol) of neat Cbz-protected amine **16** at RT was added 12 mL of 30% HBr in HOAc. The resulting mixture was stirred at RT for 1 h and then concentrated (CH_2Cl_2 added for transfer and dissolution and hexanes added for hexanes-HOAc azeotrope). The resulting red-orange solid was slurried in EtOAc and 10% aqueous $NaHCO_3$ was added until the solution became clear. The organic layer was washed with water. The combined aqueous layers were extracted three times with EtOAc, saturated with solid $(NH_4)_2SO_4$ and extracted once more with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (elution with 11:1 CH_2Cl_2-MeOH followed by 6:1 CH_2Cl_2-MeOH then 3:1 CH_2Cl_2-MeOH) gave 187 mg (38.7%) of a pale foam: R_f 0.40 (3:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 339 (M+H).

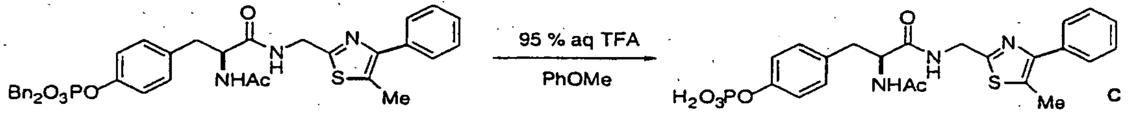
Preparation of coupling product **18**:



18

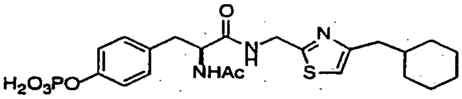
Coupling product **18** can be prepared as shown for the preparation of coupling product **6**. Flash chromatography (elution with 10:1 CH_2Cl_2-MeOH) gave 260.7 mg (51.0%) of a pale oil: R_f 0.59 (9:1 CH_2Cl_2 -MeOH).

Preparation of **C**:



To 254.7 mg (0.380 mmol) of benzyl protected phosphate **18** and 0.4 mL of anisole was added 5 mL of 95% TFA (aq). The resulting solution was stirred at RT for 2.75 h and then concentrated to a pale gold oil. White granular crystals were formed by adding Et_2O and scraping and crushing the solid in the flask. The crystals were rinsed three times with Et_2O (supernatant removed via pipet) to give 197.3 mg of a granular white solid. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 490 (M+H).

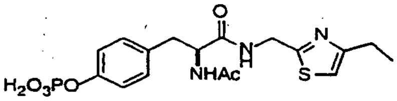
4. Compound D



D

Compounds such as Compound D can be prepared using thiazole formation Conditions A followed by Coupling Conditions C. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 496 (M+H).

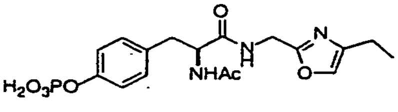
5. Compound E



E

Compounds such as Compound E can be prepared using thiazole formation Conditions B followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 854 (2M-H).

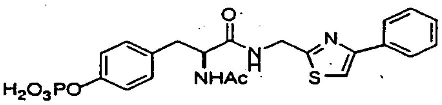
6. Compound F



F

Compounds such as Compound F can be prepared using thiazole/oxazole formation Conditions B, substituting the appropriate keto amide for the bromo ketone and substituting toluene as solvent, followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 412 (M+H).

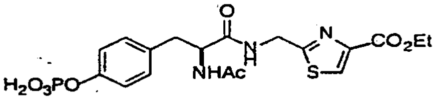
7. Compound G



G

Compounds such as Compound G can be prepared using thiazole formation Conditions B followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 476 (M+H).

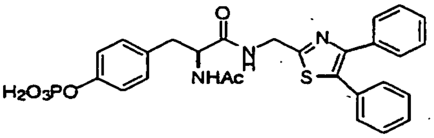
8. Compound H



H

Compounds such as Compound H can be prepared using thiazole formation Conditions B followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 472 (M+H).

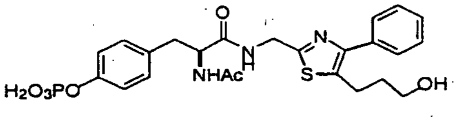
9. Compound I



I

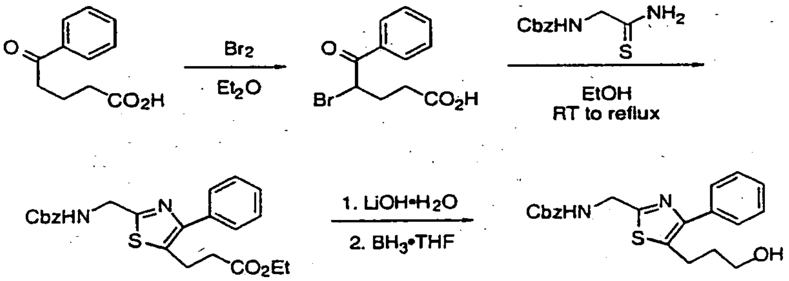
Compounds such as Compound I can be prepared using thiazole formation Conditions B followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 550 (M-H).

10. Compound J

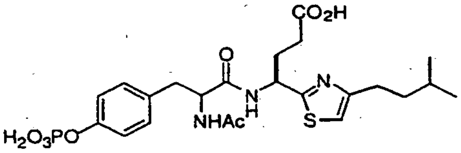


J

Compounds such as Compound J can be prepared using thiazole formation Conditions B followed by Coupling Conditions D with the appropriate side chain manipulations as shown in the following scheme. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 574 (M+CH_3CN).



11. Compound K

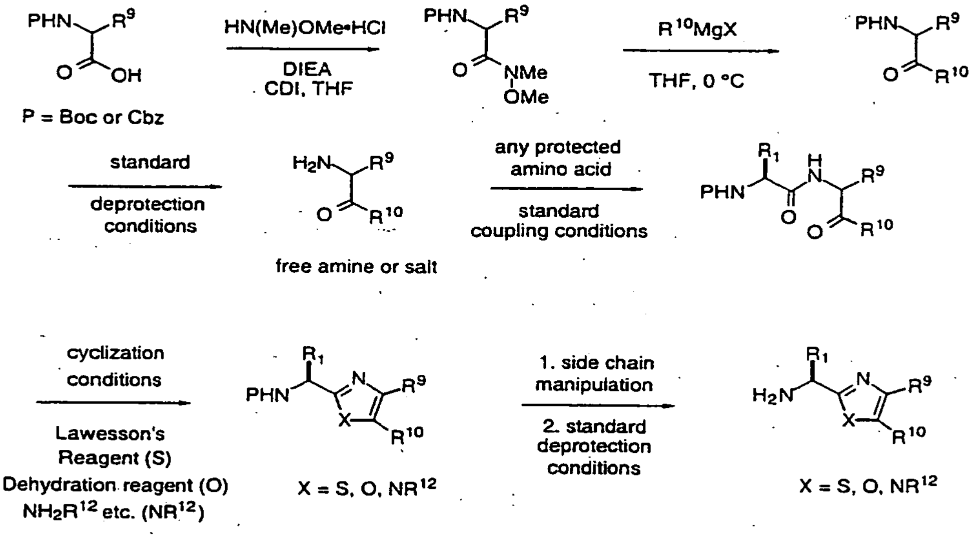


K

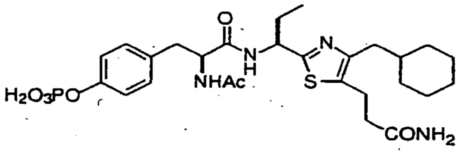
Compounds such as Compound K can be prepared using thiazole formation Conditions A followed by Coupling Conditions D. Compound K was isolated as a 60/40 mixture of diastereomers, presumably at the NHAc stereocenter. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 542 (M+H).

General Method E: Preparation of thiazoles, oxazoles and imidazoles via keto amide intermediates:

Many thiazoles, oxazoles and imidazoles can be prepared via the corresponding keto amides according to the cyclization conditions described in Gordon, T. D. et al. (*Tetrahedron Lett.* 1993, *34*, 1901) as shown generically below.



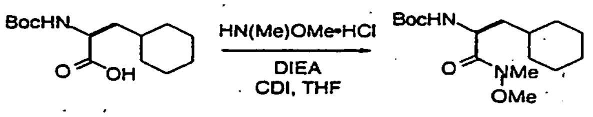
12. Compound L



L

Compounds such as Compound L can be prepared according to General Method E, followed by Coupling Conditions D. Experimental details for the synthesis of compound L are as follows:

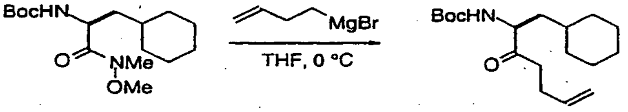
Preparation of Amide **19**:



19

To a mixture of 4.0 g (14.7 mmol) of Boc-beta-cyclohexyl-L-alanine in 75 mL of CH_2Cl_2 at 0 °C was added 2.63 g (16.2 mmol) of CDI. The resulting mixture was warmed to RT (bath removed) over 10 min whereupon 3.85 mL (22.1 mmol) of DIEA was added via syringe followed by 1.58 g (16.2 mmol) of HN(Me)OMe•HCl. The resulting mixture was stirred at RT for 22.5 h, concentrated to a viscous oil and then diluted with EtOAc and water. The organic layer was washed once with brine. The combined aqueous layers were extracted once with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (elution with EtOAc) gave 3.82 g (82.4%) of a colorless oil: R_f 0.58 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 315 (M+H).

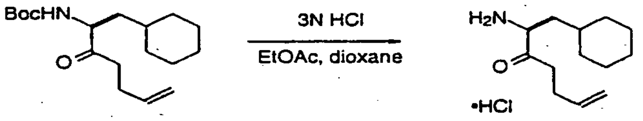
Preparation of Ketone **20**:



20

To a solution of 3.82 g (12.1 mmol) of amide **19** in 60 mL of THF at 0 °C was added 72.9 mL (36.5 mmol) of 3-butenylmagnesium bromide (0.5 M in THF). The resulting mixture was stirred at 0 °C for 10 min, and at RT for 25.5 h. The reaction was then diluted with Et_2O, quenched with saturated aqueous NH_4Cl, then diluted with more Et_2O and water. Note: At this point, the reaction mixture was combined with another reaction performed in parallel (5.66 mmol scale). The combined organic layers were washed once with brine. The combined aqueous layers were extracted twice with Et_2O. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (elution with 1:1 hexanes-EtOAc) gave 3.84 g (69.7%, combined reactions) of a pale oil: R_f 0.49 (1:1 hexanes-EtOAc).

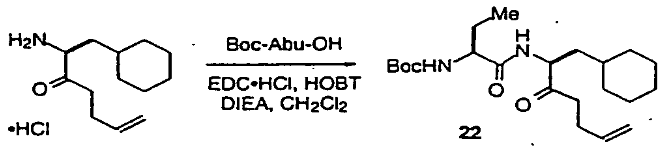
Preparation of Amine Salt **21**:



21

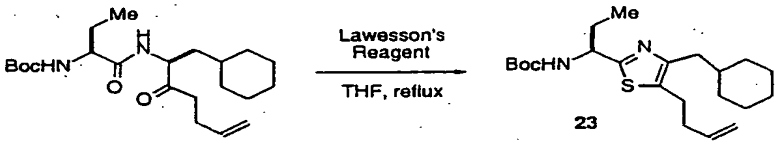
To a mixture of 3.84 g (12.4 mmol) of protected amine **20** in 20 mL of EtOAc and 20 mL of dioxane at RT was added 60 mL of 3 N HCl. The resulting mixture was stirred at RT for 4.5 days and then concentrated. The off white solid was triturated with Et_2O (3 times with decanting) and dried in vacuo giving 2.68 g (87.9%) of a fluffy white solid. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 210 (M+H).

Preparation of Ketoamide **22**:



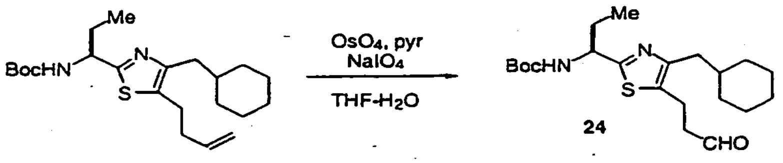
To 1.34 g (5.45 mmol) of amine salt **21** in 30 mL of CH_2Cl_2 at RT was added 3.2 mL (18.2 mmol) of DIEA followed by 0.922 g (4.54 mmol) of Boc-Abu-OH. The resulting mixture was stirred at RT for 5 min whereupon 1.043 g (6.81 mmol) of HOBT and 1.305 g (6.81 mmol) of EDC•HCl were added in one portion. The resulting mixture was stirred at RT for 23 h and then concentrated to a viscous oil. The resulting oil was then diluted with EtOAc and 5% aqueous $NaHCO_3$. The organic layer was then washed with 10% citric acid and brine. The combined aqueous layers were extracted once with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (elution with 3:1 hexanes-EtOAc) gave 1.59 g (88.8%) of a white solid: R_f 0.42 (1:1 hexanes-EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 395 (M+H).

Preparation of Thiazole **23**:



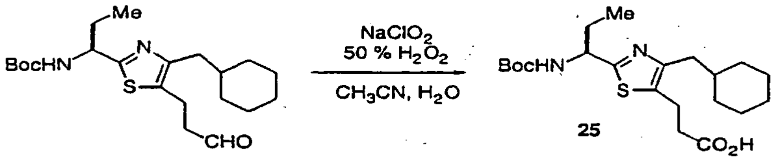
To a solution of 1.59 g (4.03 mmol) of ketoamide **22** in 20 mL of THF at RT was added 3.34 g (8.26 mmol) of Lawesson's reagent. The resulting mixture was stirred at 67 °C for 2.5 h, cooled to RT and then concentrated. Flash chromatography (elution with 3:1 hexanes-EtOAc) gave 1.28 g (81.0%) of a yellowish oil: R_f 0.60 (1:1 hexanes-EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 393 (M+H).

Preparation of Aldehyde **24**:



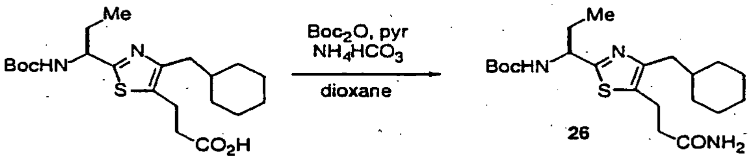
To a solution of 1.28 g (3.26 mmol) of alkene **23** in 40 mL of 1:1 THF-H_2O at RT was added 0.025 mL (0.309 mmol) of pyridine followed by 2.05 mL (0.163 mmol) of OsO_4 (2.5 wt. % in 2-methyl-2-propanol). The resulting brown mixture was stirred at RT for 10 min when 1.57 g (7.33 mmol) of $NaIO_4$ was added in 3 portions over the next 30 min. The resulting creamy tan/white slurry was stirred at RT for an additional 30 min, then diluted with Et_2O and H_2O. The organic layer was washed once each with H_2O and brine. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (elution with 2:1 hexanes-EtOAc) gave 1.01 g (78.3%) of a pale oil which turned brown upon standing: R_f 0.67 (1:1 hexanes-EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 395 (M+H).

Preparation of Acid **25**:



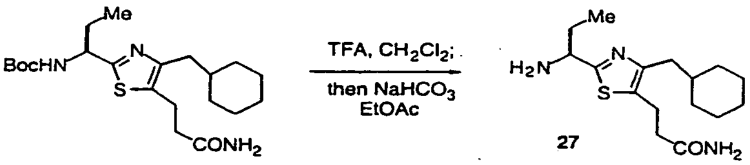
To a solution of 1.01 g (2.56 mmol) of aldehyde **24** in 7.5 mL of CH_3CN at 0 °C was added over 1 min, a solution of 0.463 g (5.12 mmol) of $NaClO_2$ in 4.5 mL H_2O followed by 1.2 mL of 50% H_2O_2. The resulting mixture was stirred at 0 °C for 10 min and at RT for 1.3 h, whereupon an additional 58 mg (0.64 mmol) of $NaClO_2$ was added. The resulting mixture was stirred at RT for an additional 40 min, quenched with solid Na_2SO_3, stirred an additional 5 min and then concentrated. The residue was diluted with EtOAc and H_2O. The organic layer was washed once with brine, dried with Na_2SO_4 and concentrated. The crude acid was used in the next step without purification: R_f 0.33 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 411 (M+H).

Preparation of Amide **26**:



To a solution of crude acid **25** in 20 mL of dioxane and 2.0 mL of pyridine at RT was added 2.79 g (12.8 mmol) of Boc_2O followed by 1.02 g (12.8 mmol) of NH_4HCO_3. The resulting mixture was stirred at RT for 13.5 h, then diluted with EtOAc and H_2O. The organic layer was washed once with brine. The combined aqueous layer and washing were extracted three times with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (elution with EtOAc) gave 0.693 g (66.1% from aldehyde **24**) of a yellowish oil: R_f 0.47 (EtOAc). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 410 (M+H).

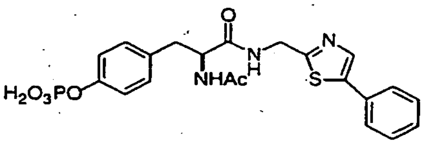
Preparation of Amine **27**:



To a solution of 693 mg (1.69 mmol) of protected amine **26** in 15 mL of CH_2Cl_2 at RT was added 3 mL of TFA. The resulting mixture was stirred at RT for 2 h and then concentrated. To the resulting viscous residue was added EtOAc and H_2O followed by 10% aqueous $NaHCO_3$ until pH paper indicated the aqueous phase was slightly basic. The organic layer was washed once with brine. The combined aqueous layer and washing were extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated giving 483 mg (92.2%) of a gold solid: R_f 0.14 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 310 (M+H).

Compound L can then be prepared using amine **27** according to Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 595 (M+H).

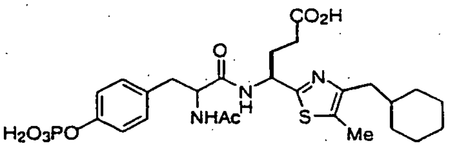
13. Compound M



M

Compounds such as Compound M can be prepared using General Method E using the commercially available amino ketone followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 476 (M+H).

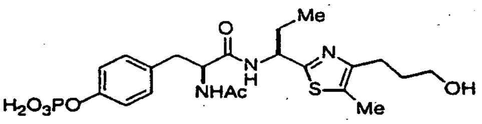
14. Compound N



N

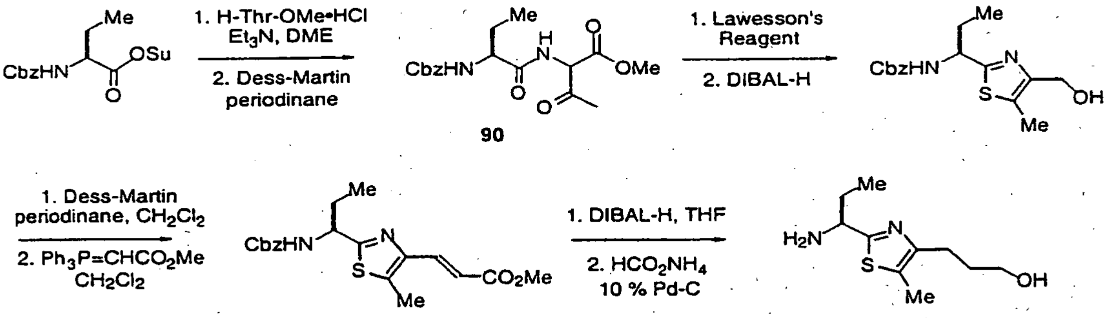
Compounds such as Compound N can be prepared using General Method E followed by Coupling Conditions D. Compound N was isolated as a 60/40 mixture of diastereomers, presumably at the NHAc stereocenter. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 582 (M+H).

15. Compound O

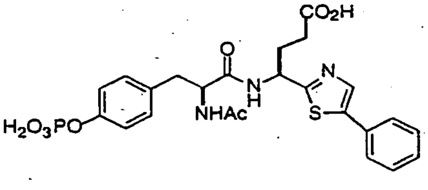


O

Compounds such as Compound O can be prepared using General Method E followed by Coupling Conditions D with the appropriate side chain manipulations as shown in the following scheme. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 500 (M+H).



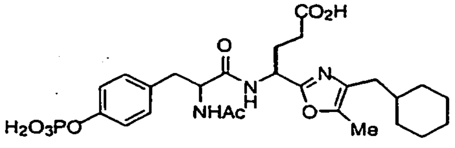
16. Compound P



P

Compounds such as Compound P can be prepared using General Method E using the commercially available amino ketone followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 546 (M-H).

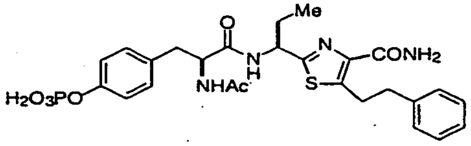
17. Compounds Q



Q

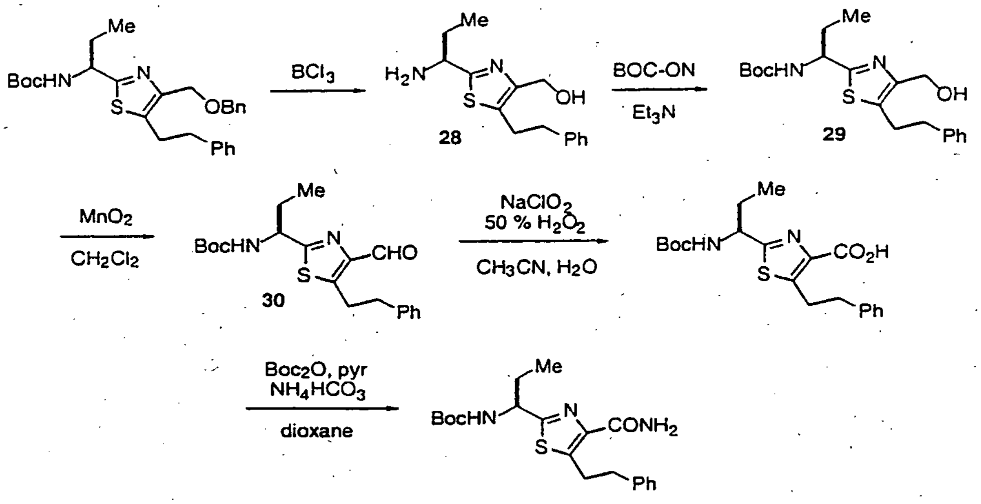
Compounds such as Compound Q can be prepared using General Method E followed by Coupling Conditions D. Reverse phase HPLC resulted in the separation of two diastereomers, presumably at the NHAc stereocenter. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 566 (M+H).

18. Compound R

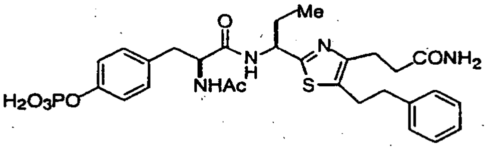


R

Compounds such as Compound R can be prepared using General Method E followed by Coupling Conditions D with the appropriate side chain manipulations as shown in the following scheme. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 575 (M+H).

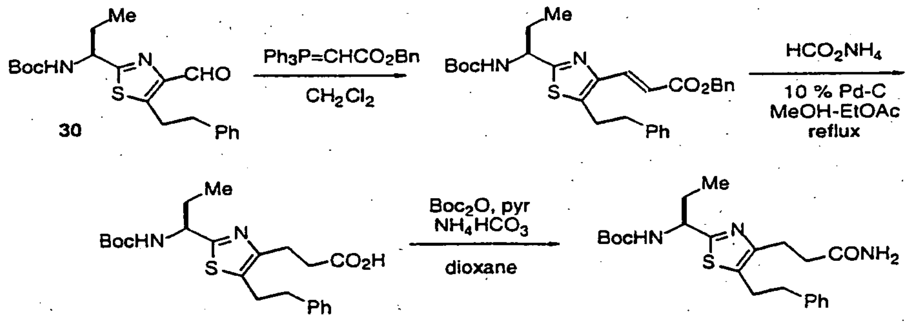


19. Compound S

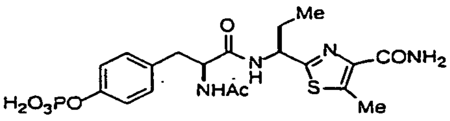


S

Compounds such as Compound S can be prepared using General Method E followed by Coupling Conditions D with the appropriate side chain manipulations included according to the following scheme using the aldehyde (**30**) described for the preparation of compound R. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 603 (M+H).

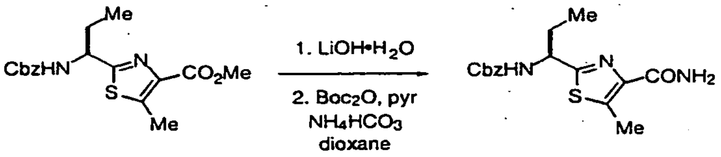


20. Compound T

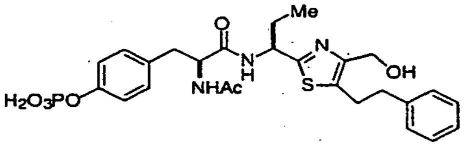


T

Compounds such as Compound T can be prepared using General Method E followed by Coupling Conditions D similar to the preparation of Compound O with the appropriate side chain manipulations as shown in the following scheme. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 485 (M+H).

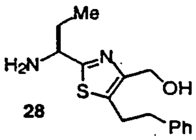


21. Compound U



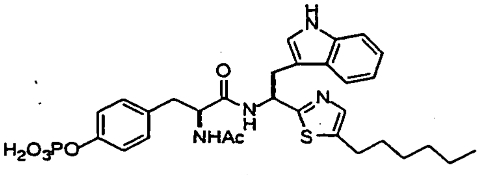
U

Compounds such as Compound U can be prepared using General Method E followed by Coupling Conditions D using the amino alcohol 28 formed in the preparation of Compound R and shown below. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 562 (M+H).



28

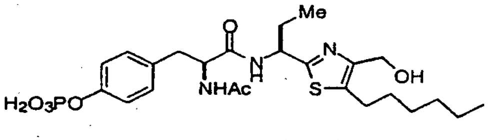
22. Compound V



V

Compounds such as Compound V can be prepared using General Method E followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 614 (M+H).

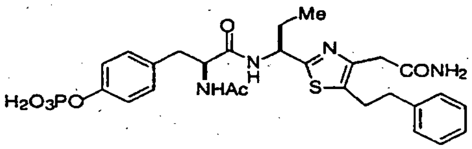
23. Compound W



W

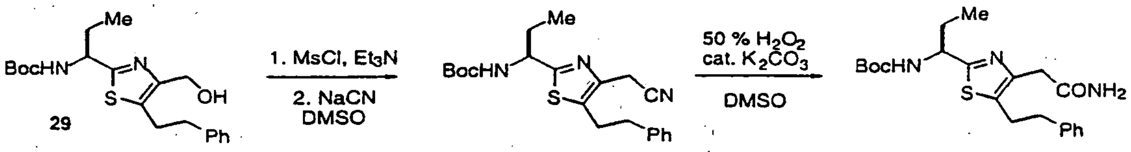
Compounds such as Compound W can be prepared using General Method E followed by Coupling Conditions D using the appropriate amino alcohol as described in the preparation of Compounds U and R. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 542 (M+H).

24. Compound X

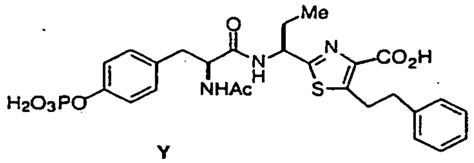


X

Compounds such as Compound X can be prepared using General Method E followed by Coupling Conditions D with the appropriate side chain manipulations as shown in the following scheme using the intermediate alcohol **29** found in the preparation of Compound R. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 589 (M+H).

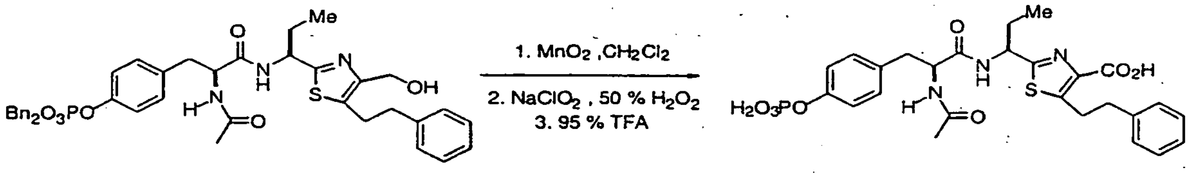


25. Compound Y

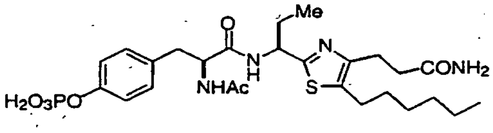


Y

Compounds such as Compound Y can be prepared using amino alcohol **28**, prepared using General Method E as found in the preparation of Compound U, followed by Coupling Conditions D with the appropriate side chain manipulations as shown in the following scheme. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 576 (M+H).



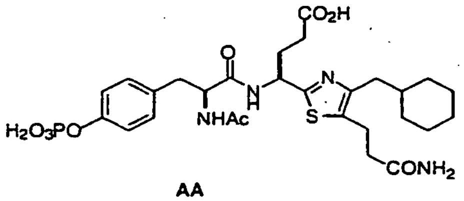
26. Compound Z



Z

Compounds such as Compound Z can be prepared using General Method E followed by Coupling Conditions D along with the appropriate side chain manipulations as shown in the scheme shown for the preparation of Compound S. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 583 (M+H).

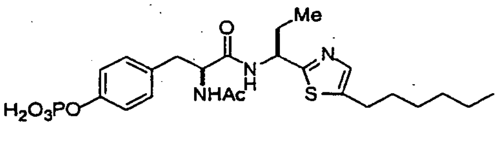
27. Compound AA



AA

Compounds such as Compound AA can be prepared using General Method E followed by Coupling Conditions D with the appropriate side chain manipulations analogous to those shown for the preparation of Compound L. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 637 (M-H).

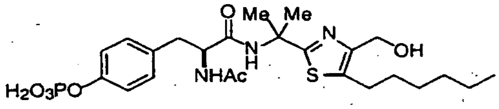
28. Compound AB



AB

Compounds such as Compound AB can be prepared using General Method E followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 512 (M+H).

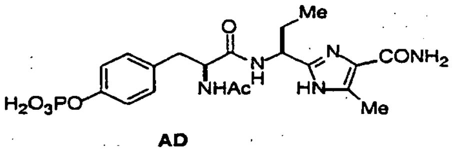
29. Compound AC



AC

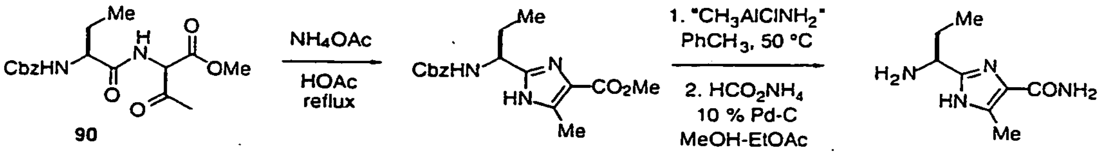
Compounds such as Compound AC can be prepared using General Method E followed by Coupling Conditions D using the appropriate amino alcohol as in the preparation of Compounds U and W. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 542 (M+H).

29B. Compound AD

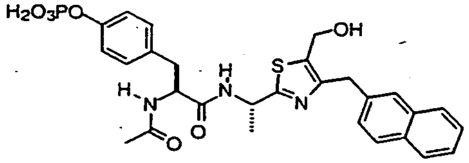


AD

Compounds such as Compound AD can be prepared using General Method E followed by Coupling Conditions D similar to the preparation of Compound O with the appropriate side chain manipulations as shown in the following scheme. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 466 (M-H).

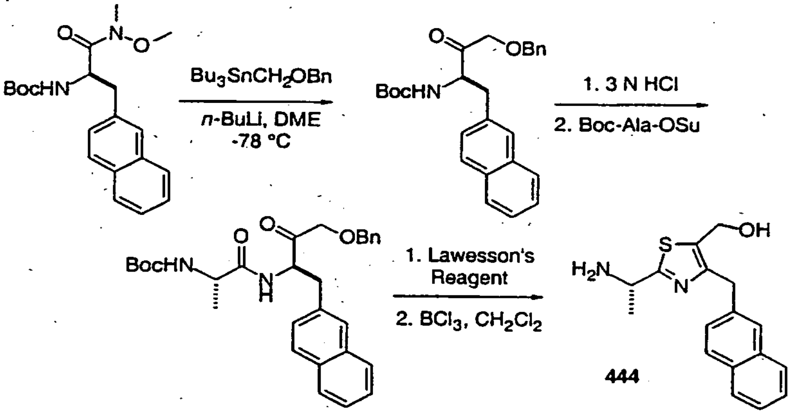


29C. Compound AE

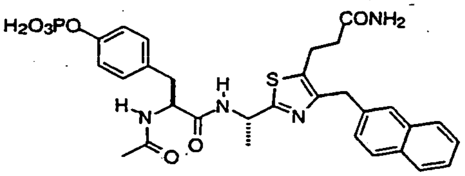


AE

Compounds such as Compound AE can be prepared using General Method E followed by Coupling Conditions D as in the preparation of Compounds U and W, using the appropriate amino alcohol which can be prepared as shown in the scheme below. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 582 (M-H).



29D. Compound AF



AF

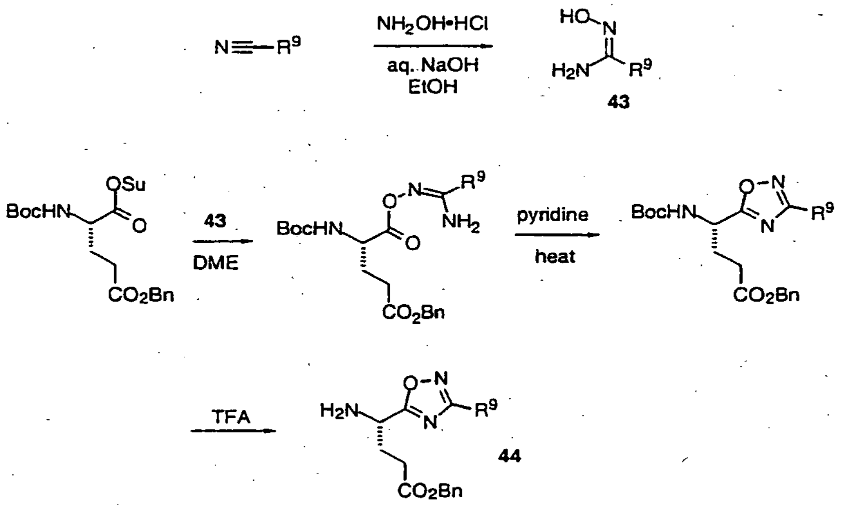
Compounds such as Compound AF can be prepared using General Method E followed by Coupling Conditions D with side chain manipulations as shown for the preparation of

Compounds R and S, using the appropriate amino alcohol (**444**), which can be prepared as previously described in the preparation of Compound AE. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 625 (M+H).

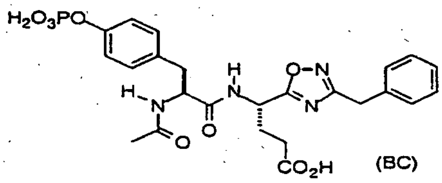
General Method F: Preparation of oxadiazoles - hydrogenation procedure:

Many oxadiazoles can be prepared via cyclization of the appropriate O-acylamidoxime according to the method described in Borg et al. (*J. Org. Chem.* **1995**, *60*, 3112). The required amidoxime can be prepared via the corresponding nitrile as shown below. The resulting amine can then be further elaborated according to Coupling Conditions D.

The general scheme shown below can be used for the preparation of compounds such as Compounds BA-BH and is exemplified by the preparation of Compound BC.

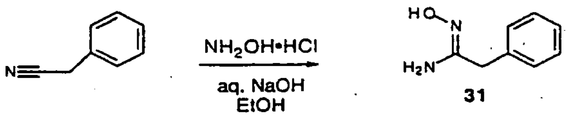


30. Compound BC



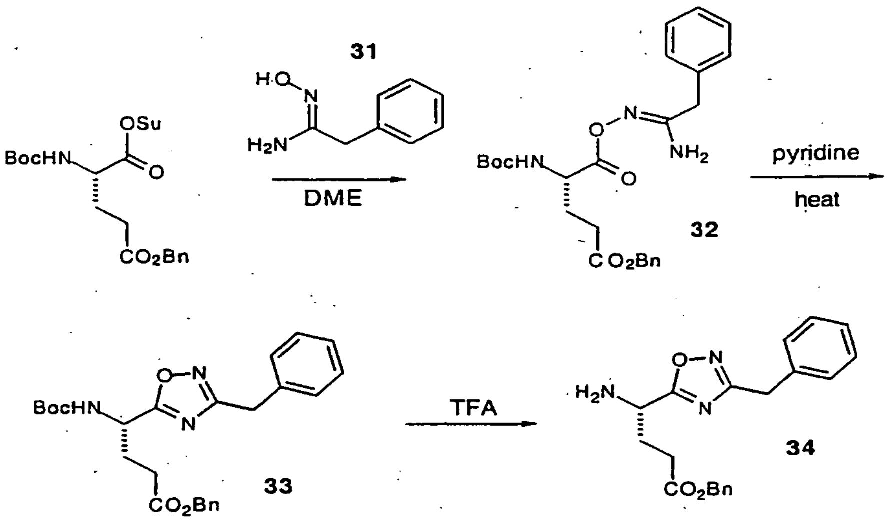
(BC)

Preparation of Amidoxime 31:



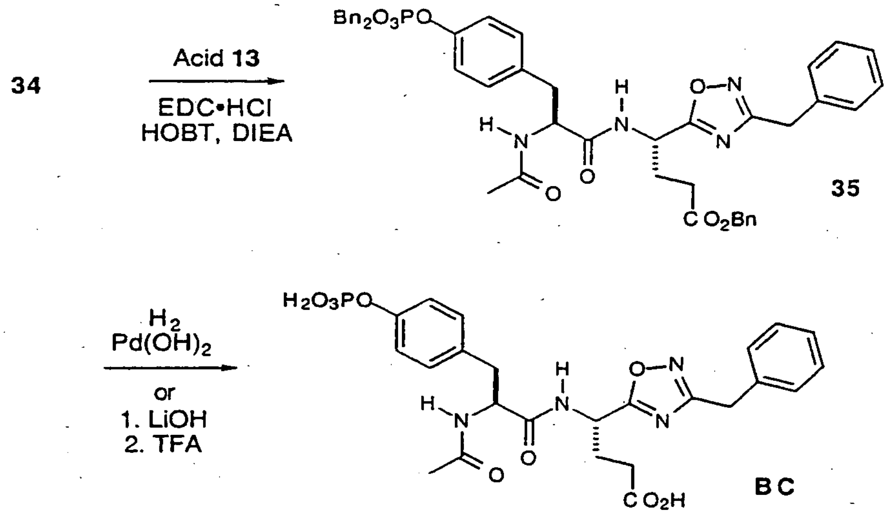
In a typical procedure, benzyl cyanide (0.03755 mol) was dissolved in 80 mL of EtOH. A solution of hydroxylamine hydrochloride (0.04506 mol) and NaOH (0.04506 mol) in 20 mL of water was added and the resulting reaction mixture was heated at reflux for two days. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to remove the volatile solvent. The resulting residue was diluted with 50 mL of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give 5.30 g of product **31**.

Preparation of Amine **34**:



In a typical procedure, Boc-Glu(OBn)-OSu (500 mg, 1.15 mmol) was dissolved in 7 mL of ethylene glycol dimethyl ether along with 1.15 mmol of amidoxime **31**. The resulting reaction mixture was stirred at rt for 15 h. It was then concentrated under reduced pressure. The resulting residue was taken up in EtOAc and washed with dilute $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the intermediate product **32**. This material was dissolved in 4 mL of pyridine and heated at reflux for 30 min. The reaction mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with 10% citric acid to remove all the pyridine. It was then washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give protected oxadiazole **33**. The resulting residue was dissolved in 6 mL of 25% TFA in CH_2Cl_2 and allowed to stand at rt for 3 h. It was then concentrated under reduced pressure. The light yellow, gummy solid was taken up in EtOAc and carefully neutralized with dilute $NaHCO_3$. The organic layer was then washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 350 mg of product **34**.

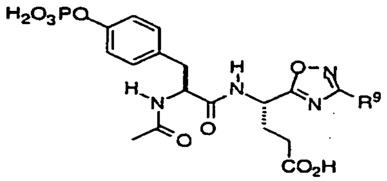
Preparation of **BC**:



In a typical procedure (analogous to Coupling Conditions D), 252 mg of acid **13** (0.523 mmol) was dissolved in 5 mL of CH_2Cl_2 and 1 mL of DMF along with 220 mg of amine **34** (0.627 mmol). HOBT (96 mg, 0.627 mmol) and EDC•HCl (120 mg, 0.627 mmol) were added at rt. After 0.136 mL of DIEA (0.784 mmol) was added, the resulting reaction mixture was stirred at rt for 4 h. It was then concentrated under reduced pressure. The resulting residue was taken up in EtOAc and washed successively with dilute $NaHCO_3$, brine, 10% citric acid and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 410 mg of product **35**. A portion of product **35** (100 mg, 0.122 mmol) was dissolved in 3 mL of MeOH and 3 mL of EtOAc. A catalytic amount of 20% $Pd(OH)_2$ over activated carbon (30 mg) was added and the resulting reaction mixture was hydrogenated at rt under atmospheric pressure using a hydrogen balloon for 40 min. The reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure. The resulting crude product was purified by preparative HPLC using aqueous CH_3CN containing 0.1% TFA to afford 12 mg of oxadiazole product **BC** (retention time = 18 min; solvent gradient = 0 min, 95:5 H_2O/CH_3CN; 5 min, 95:5 H_2O/CH_3CN; 25 min, 50:50 H_2O/CH_3CN, 50 min, 0:100 H_2O/CH_3CN). Electrospray mass spectrum (50:50 H_2O/CH_3CN + 0.1% aq NH_4OH) m/z 545 (M-H). ^1H NMR (DMSO) d 1.8 (s, 3 H), 2-2.5 (m, 6 H), 4.15 (s, 2 H), 4.4-4.5 (m, 1 H), 5.1-5.2 (m, 1 H), 7-7.6 (m, 9 H), 8.0-8.1 (m, 1 H), 8.7-8.8 (m, 1 H).

31. Compounds BA-BH

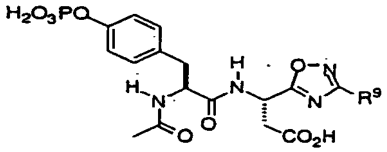
Compounds such as Compounds BA-BH can be prepared according to General Method F as exemplified above for the preparation of Compound BC.



Compound	R^9	MS
BA	-CH_2Chx	552 (M-H)
BB	-$(CH_2)_2CH(CH_3)_2$	525 (M-H)
BC	-CH_2Ph	545 (M-H)
BD	-$CH_2CH(CH_3)_2$	511 (M-H)
BE	-CH_2-cyclopropyl	509 (M-H)
BF	-$(CH_2)_6CH_3$	554 (M-H)
BG	-$(CH_2)_4CH_3$	525 (M-H)
BH	-$(CH_2)_5CH_3$	562 (M+MeCN)

31A. Compounds BN-BW

Similarly, compounds such as Compounds BN-BW can be prepared according to General Method F as exemplified above for the preparation of Compound BC.



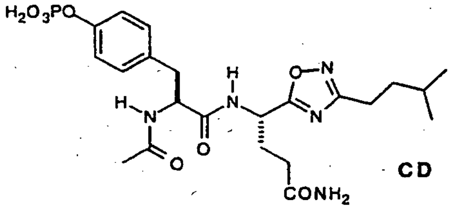
Compound	R^9	MS
BN	-$CH_2(C_6H_4)$-4-Cl	565 (M-H)
BO	-CH_2-(2-naphthyl)	581 (M-H)
BP	-$CH_2(C_6H_4)$-4-CF_3	599 (M-H)
BQ	-$CH_2(C_6H_4)$-4-OCH_3	561 (M-H)
BR	-$CH_2(C_6H_4)$-4-F	549 (M-H)

BS	-$CH_2(C_6H_4)$-3,4-Cl_2	600 (M-H)
BT	-$CH_2(C_6H_4)$-4-CH_3	545 (M-H)
BU	-$CH_2(C_6H_4)$-4-Br	610 (M-H)
BV	-$CH_2(C_6H_4)$-3-Cl	566 (M-H)
BW	-$CH_2(C_6H_4)$-3-CF_3	599 (M-H)

General Method G: Preparation of oxadiazoles - TFA procedure:

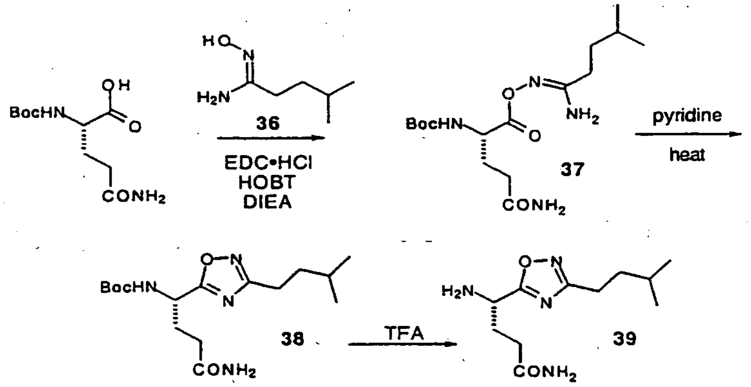
Compounds such as Compounds CA-FBG and GA-GC can be prepared according to General Method F followed by Coupling Conditions D as exemplified below by the preparation of Compound CD.

32. Compound CD



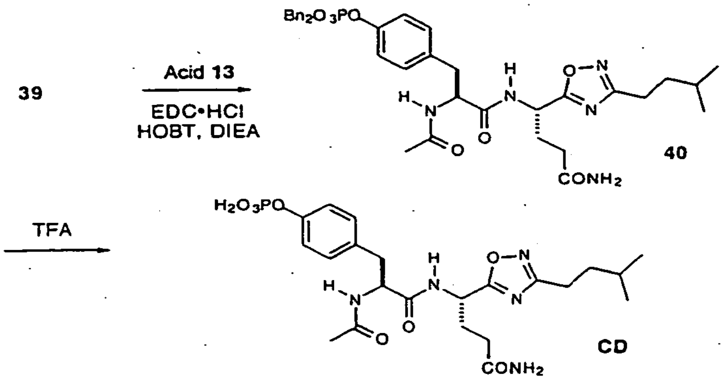
CD

Preparation of amine **39**:



Amidoxime **36** was prepared using the same procedure that was outlined for compound **BC** substituting isovaleronitrile. Amidoxime **36** (150 mg, 1.15 mmol) was then dissolved in 2 mL of DMF and 6 mL of CH_2Cl_2 along with Boc-Gln-OH (237 mg, 0.958 mmol). HOBT (176 mg, 1.15 mmol) and EDC•HCl (220 mg, 1.15 mmol) were added. followed by DIEA (0.25 mL, 1.44 mmol). The resulting reaction mixture was stirred at rt for 8 h. It was then concentrated under reduced pressure and then redissolved in 50 mL of EtOAc. The organic layer was washed with dilute aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated under reduced pressure to obtain 245 mg of product **37**. Compound **37** was then subjected to the same reaction sequence outlined in the preparation of compound **BC** in order to obtain 95 mg of compound **39**.

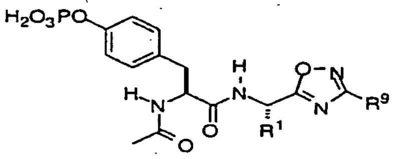
Preparation of compound **CD**:

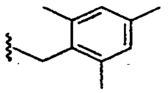
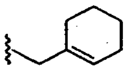
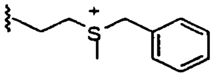


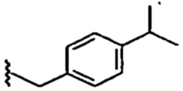
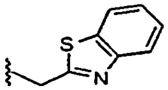
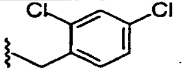
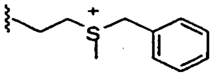
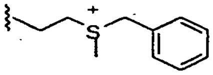
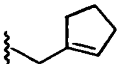
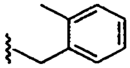
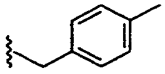
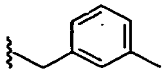
In a typical procedure, 150 mg of acid **13** (0.313 mmol) was dissolved in 5 mL of CH_2Cl_2 and 1 mL of DMF along with 90 mg of amine **39** (0.375 mmol). HOBT (57 mg, 0.375 mmol) and EDC•HCl (72 mg, 0.375 mmol) were added at rt. After 0.082 mL of DIEA (0.470 mmol) was added, the resulting reaction mixture was stirred at rt for 4 h. It was then concentrated under reduced pressure. The resulting residue was taken up in EtOAc and washed successively with dilute $NaHCO_3$, brine, 10% citric acid and brine. The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure to give 190 mg of product **40**. This material was dissolved in 4 mL of a solution containing 95% TFA, 2.5% H_2O, 2.5% anisole. The resulting reaction mixture was allowed to stand at rt for 2h. It was then concentrated and the crude product **CD** was precipitated out as a solid using Et_2O. A portion of this crude product was purified by preparative HPLC using aqueous CH_3CN containing 0.1% TFA to afford 9 mg of oxadiazole **CD** (retention time = 20 min; solvent gradient = 0 min, 95:5 H_2O/CH_3CN; 5 min, 95:5 H_2O/CH_3CN; 25 min, 60:40 H_2O/CH_3CN, 50 min, 0:100 H_2O/CH_3CN). Electrospray mass spectrum (50:50 H_2O/CH_3CN + 0.1% aq NH_4OH) m/z 525 (M-H). ^{1}H NMR (DMSO) d 0.8 (s, 3H), 0.85 (s, 3 H), 1.3-2.5 (m, 11 H), 1.7 (s, 3 H), 4.3-4.4 (m, 1 H), 5.0-5.1 (m, 1 H), 6.8 (br s, 1 H), 7.0 (d, 2 H), 7.15 (d, 2 H), 7.25 (br s, 1 H), 8.0-8.1 (m, 1 H), 8.8-8.9 (m, 1 H).

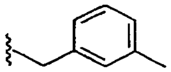
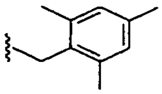
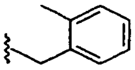
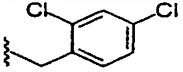
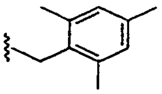
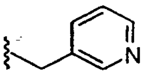
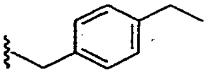
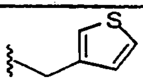
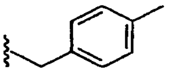
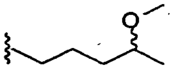
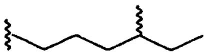
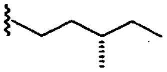
33. Compounds CA-FBG

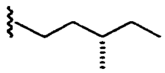
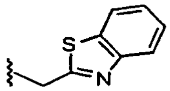
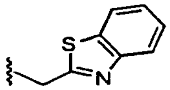
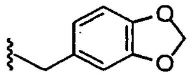
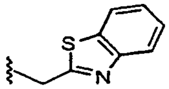
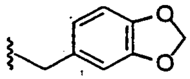
Compounds such as Compounds CA-FBG can be prepared according to General Method G as exemplified above for the preparation of Compound CD.

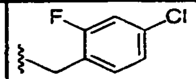


Compound	R^1	R^9	MS
CA	$-(CH_2)_2CO_2CH_2Ph$	$-CH_2CH(CH_3)_2$	601 (M-H)
CB	$-(CH_2)_2CONH_2$	$-CH_2Ph$	545 (M-H)
CC	$-(CH_2)_2CONH_2$	$-CH_2Chx$	550 (M-H)
CD	$-(CH_2)_2CONH_2$	$-(CH_2)_2CH(CH_3)_2$	525 (M-H)
CE	$-CH_2(C_6H_4)$-4-OH	$-CH_2Ph$	579 (M-H)
CF	$-CH_2(C_6H_4)$-4-OH	$-CH_2Chx$	586 (M-H)
CG	$-CH_2Ph$	$-CH_2Ph$	563 (M-H)
CH	$-CH_2Ph$	$-CH_2Chx$	569 (M-H)
CI	$-CH_2(C_6H_4)$-4-OH	$-(CH_2)_2CH(CH_3)_2$	560 (M-H)
CJ	$-CH_2Ph$	$-(CH_2)_2CH(CH_3)_2$	543 (M-H)
CK	$-(CH_2)_2CONH_2$		586 (M-H)
CL	H	$-CH_2Chx$	479 (M-H)
CM	$-(CH_2)_2CONH_2$	$-(CH_2)_3CH_3$	511 (M-H)
CN	$-(CH_2)_2CONH_2$	-Ph	530 (M-H)
CO	$-(CH_2)_2CONH_2$		548 (M-H)
CP	$-(CH_2)_2CONH_2$	$-(CH_2)_5CH_3$	538 (M-H)
CQ	-Ph	$-CH_2Ph$	549 (M-H)
CR	$-(CH_2)_3CH_3$	$-CH_2Ph$	529 (M-H)
CS		$-CH_2Ph$	639 (M-H)
CT	$-(CH_2)_2SO_2CH_3$	$-(CH_2)_2CH(CH_3)_2$	561 (M-H)
CU	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-4-CF_3	607 (M-H)
CV	$-CH_2CH_3$	$-(CH_2)_2CH(CH_3)_2$	481 (M-H)

CW	-$(CH_2)_2CONH_2$		586 (M-H)
CX	-$(CH_2)_2CONH_2$		601 (M-H)
CY	-$(CH_2)_2CONH_2$	-CH_2-(1-naphthyl)	595 (M-H)
CZ	-$(CH_2)_2CONH_2$		613 (M-H)
DA	-$(CH_2)_3CH_3$	-$(CH_2)_2CH(CH_3)_2$	509 (M-H)
DB	-CH_2-(3-indole)	-$(CH_2)_2CH(CH_3)_2$	582 (M-H)
DC	-Ph	-CH_2Chx	555 (M-H)
DD	-$CH_2CH(CH_3)_2$	-CH_2Chx	536 (M-H)
DE	-$(CH_2)_3CH_3$	-CH_2Chx	535 (M-H)
DF	-CH_2-(3-indole)	-CH_2Chx	609 (M-H)
DG	-CH_2CH_3	-CH_2Ph	502 (M-H)
DH	-$(CH_2)_2SCH_3$	-$(CH_2)_2CH(CH_3)_2$	527 (M-H)
DI		-$(CH_2)_2CH(CH_3)_2$	618 (M-H)
DJ	-$CH_2CH(CH_3)_2$	-CH_2Ph	529 (M-H)
DK	-CH_2-(3-indole)	-CH_2Ph	603 (M-H)
DL	-$CH_2CH(CH_3)_2$	-$(CH_2)_2CH(CH_3)_2$	509 (M-H)
DM	-$(CH_2)_2CONH_2$	-$CH_2(C_6H_4)$-4-OCH_3	574 (M-H)
DN	-$(CH_2)_2CONH_2$	-$(CH_2)_2$Ph	558 (M-H)
DO	-$(CH_2)_2SCH_3$	-CH_2Chx	553 (M-H)
DP		-CH_2Chx	645 (M-H)
DQ	-Ph	-$(CH_2)_2CH(CH_3)_2$	529 (M-H)
DR	-$(CH_2)_2CONH_2$		534 (M-H)
DS	-$(CH_2)_2CONH_2$	-$(CH_2)_3CCH$	522 (M+H)
DT	-$(CH_2)_2CONH_2$	-$(CH_2)_3CH=CH_2$	524 (M+H)
DU	-$CH_2CH(CH_3)_2$		544 (M-H)
DV	-$CH_2CH(CH_3)_2$		544 (M-H)
DW	-CH_2-(3-indole)		543 (M-H)

DX	$-CH_2CH(CH_3)_2$		544 (M-H)
DY	$-CH_2CH(CH_3)_2$		572 (M-H)
DZ	$-(CH_2)_2CONH_2$	$-(CH_2)_6CH_3$	552 (M-H)
EA	$-CH_2$-(3-indole)		617 (M-H)
EB	$-CH_2$-(3-indole)	$-CH_2$-(1-naphthyl)	653 (M-H)
EC	$-CH_2$-(3-indole)		671 (M-H)
ED	$-CH_2$-(3-indole)		645 (M-H)
EE	$-CH_2$-(3-indole)	$-(CH_2)_4CH_3$	583 (M-H)
EF	$-CH_2$-(3-indole)	$-(CH_2)_5CH_3$	597 (M-H)
EG	$-(CH_2)_2CONH_2$		547 (M+H)
EH	$-(CH_2)_2CONH_2$		575 (M+H)
EI	$-CH_2$-(3-indole)		609 (M-H)
EJ	$-CH_2$-(3-indole)	$-CH_2$-(2-naphthyl)	653 (M-H)
EK	$-CH_2$-(3-indole)		617 (M-H)
EL	$-CH_2$-(3-indole)	$-(CH_2)_6CH_3$	611 (M-H)
EM	$-CH_2$-(3-indole)		613 (M-H)
EN	$-CH_2$-(3-indole)		611 (M-H)
EO	$-CH_2$-(3-indole)	$-(CH_2)_3CH(CH_3)_2$	599 (M-H)
EP	$-CH_2$-(3-indole)		597 (M-H)
EQ	$-CH_2CH_3$	$-(CH_2)_4CH_3$	482 (M-H)
ER	$-CH_2CH_3$	$-(CH_2)_5CH_3$	496 (M-H)
ES	$-CH_2CH_3$	$-(CH_2)_6CH_3$	509 (M-H)
ET	$-CH_3$	$-CH_2$Chx	493 (M-H)
EU	$-CH_3$	$-(CH_2)_5CH_3$	481 (M-H)
EV	$-CH_2(C_6H_4)$-4-OH	$-(CH_2)_5CH_3$	574 (M-H)
EW	$-CH_2(C_6H_4)$-4-OPO_3H_2	$-(CH_2)_5CH_3$	653 (M-H)

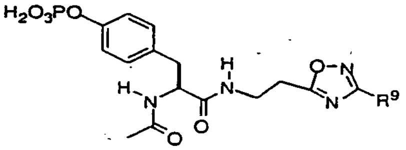
EX	-CH_3	-$(CH_2)_6CH_3$	495 (M-H)
EY	-$CH_2(C_6H_4)$-4-OH	-$(CH_2)_6CH_3$	587 (M-H)
EZ	-CH_3	-CH_2Ph	488 (M-H)
FA	-$CH_2(C_6H_4)$-4-OPO_3H_2	-$(CH_2)_6CH_3$	667 (M-H)
FB	-CH_3	-$(CH_2)_4CH_3$	467 (M-H)
FC	-CH_3		482 (M-H)
FD	-CH_3		530 (M-H)
FE	-CH_3	-CH_2-(2-naphthyl)	538 (M-H)
FF	-CH_2CONH_2	-CH_2-(2-naphthyl)	580 (M-H)
FG	-CH_2CONH_2	-$CH_2(C_6H_4)$-4-CF_3	599 (M-H)
FH	-CH_3	-$CH_2(C_6H_4)$-4-CF_3	556 (M-H)
FI	-CH_2CONH_2	-$CH_2(C_6H_4)$-4-OCH_3	560 (M-H)
FJ	-CH_2CONH_2		588 (M-H)
FK	H	-$CH_2(C_6H_4)$-4-OCH_3	503 (M-H)
FL	H	-$CH_2(C_6H_4)$-4-CF_3	541 (M-H)
FM	H	-$CH_2(C_6H_4)$-4-Cl	508 (M-H)
FN	-CH_2CONH_2	-$CH_2(C_6H_4)$-4-Cl	565 (M-H)
FO	-CH_2CONH_2		574 (M-H)
FP	H		531 (M-H)
FQ	H	-CH_2-(2-naphthyl)	524 (M-H)
FR	-$(CH_2)_2CONH_2$		588 (M-H)
FS	-CH_2CN	-$CH_2(C_6H_4)$-4-CF_3	580 (M-H)
FT	-CH_3	-$CH_2(C_6H_4)$-4-CH_3	501 (M-H)
FU	-CH_3	-$CH_2(C_6H_4)$-4-Cl	522 (M-H)
FV	-$(CH_2)_2CONH_2$	-$CH_2(C_6H_4)$-4-Cl	579 (M-H)
FW	-CH_3	-$CH_2(C_6H_4)$-3,4-Cl_2	555 (M-H)
FX	-CH_3	-$(CH_2)_5CH_3$	467 (M+H)
FY	-CH_2OH	-$CH_2(C_6H_4)$-4-CF_3	571 (M-H)
FZ	-CH_2CONH_2	-$CH_2(C_6H_4)$-4-CH_3	546 (M+H)

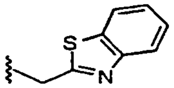
FAA	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-4-CH_3	558 (M-H)
FAB	$-CH_3$	$-CH_2(C_6H_4)$-3,4-$(OMe)_2$	547 (M-H)
FAC	$-CH_3$	$-CH_2(C_6H_4)$-3-Cl	521 (M-H)
FAD	$-CH_3$	$-CH_2(C_6H_4)$-3-CF_3	555 (M-H)
FAE	$-CH_2CONH_2$	$-CH_2(C_6H_4)$-3,4-Cl_2	598 (M-H)
FAF	$-CH_2CONH_2$	$-CH_2(C_6H_4)$-3-Cl	566 (M+H)
FAG	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-3,4-Cl_2	614 (M+H)
FAH	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-3-Cl	578 (M-H)
FAI	$-CH_2OH$	$-CH_2(C_6H_4)$-3,4-Cl_2	571 (M-H)
FAJ	$-CH_2CONH_2$	$-CH_2(C_6H_4)$-3,4-$(OMe)_2$	592 (M+H)
FAK	-geminal-Me_2	$-CH_2(C_6H_4)$-4-CF_3	571 (M+H)
FAL	$-CH_3$	$-CH_2(C_6H_4)$-4-F	505 (M-H)
FAM	$-CH_2CONH_2$	$-CH_2(C_6H_4)$-3-CF_3	600 (M+H)
FAN	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-3-CF_3	614 (M+H)
FAO	$-CH_3$	$-CH_2(C_6H_4)$-4-I	613 (M-H)
FAP	$-CH_3$		540 (M-H)
FAQ	$-CH_3$	$-CH_2(C_6H_4)$-3,4-F_2	523 (M-H)
FAR	$-CH_3$	$-CH_2(C_6H_4)$-3,5-Cl_2	556 (M-H)
FAS	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-4-Br	622 (M-H)
FAT	$-CH_2OH$	$-CH_2(C_6H_4)$-4-F	523 (M+H)
FAU	$-CH_2CH_3$	$-CH_2(C_6H_4)$-3,4-Cl_2	571 (M+H)
FAV	$-CH_2OH$	$-CH_2(C_6H_4)$-4-Cl	539 (M+H)
FAW	$-CH_2OH$	$-CH_2$-(2-naphthyl)	555 (M+H)
FAX	$-CH(OH)CH_3$	$-CH_2(C_6H_4)$-4-Br	597 (M+H)
FAY	$-CH_3$	$-CH_2(C_6H_4)$-4-Br	566 (M-H)
FAZ	$-(CH_2)_2Ph$	$-CH_2(C_6H_4)$-4-CF_3	645 (M-H)
FBA	$-(CH_2)_2Ph$	$-CH_2(C_6H_4)$-4-(O-*n*-Pr)	635 (M-H)
FBB	$-(CH_2)_2Ph$	$-CH_2(C_6H_4)$-3,4-Cl_2	645 (M-H)
FBC	$-CH_2OH$	$-CH_2(C_6H_4)$-3-Cl, 4-I	662 (M-H)
FBD	$-CH_2OH$	$-CH_2(C_6H_4)$-4-Br	565 (M-H)
FBE	$-CH_3$	$-CH_2(C_6H_4)$-3-Cl, 4-I	647 (M-H)

FBF	-$(CH_2)_2CONH_2$	-CH_2-(2-naphthyl)	594 (M-H)
FBG	-$(CH_2)_2Ph$	-CH_2-(2-naphthyl)	627 (M-H)

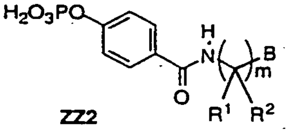
34. Compounds GA-GC

Compounds such as Compounds GA-GC can be prepared using General Methods F and G using the appropriate nitrile and with the substitution of beta alanine for a typical alpha amino acid.



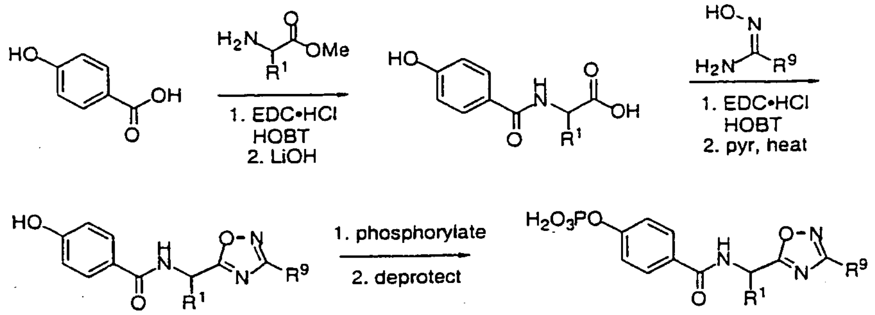
Compound	R^9	MS
GA	-$CH_2(C_6H_4)$-4-CF_3	555 (M-H)
GB	-CH_2-(2-naphthyl)	537 (M-H)
GC		544 (M-H)

General Method H: Preparation of benzamides:

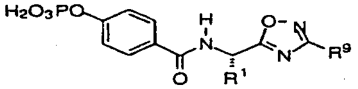


ZZ2

Compounds such as Compound ZZ2 can be prepared according to the scheme below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example.



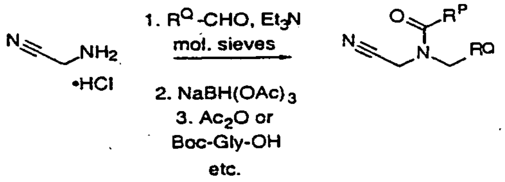
35. Compounds HA-HG



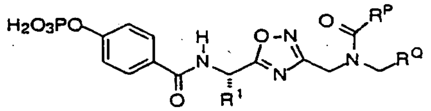
Compound	R^1	R^9	MS
HA	$-(CH_2)_2CO_2H$	$-(CH_2)_2CH(CH_3)_2$	440 (M-H)
HB	$-CH_2CH_3$	$-(CH_2)_2CH(CH_3)_2$	396 (M-H)
HC	$-CH_2CH_3$	$-(CH_2)_6CH_3$	424 (M-H)
HD	$-(CH_2)_2CO_2H$	$-(CH_2)_6CH_3$	468 (M-H)
HE	$-CH_2CH_3$	$-(CH_2)_2Ph$	430 (M-H)
HF	$-(CH_2)_2CO_2H$	$-(CH_2)_2Ph$	474 (M-H)
HG	$-(CH_2)_2CO_2Me$	$-(CH_2)_2Ph$	488 (M-H)

General Method I: Preparation of branched benzamides:

Compounds such as Compounds IA-IC can be prepared according to General Methods F, G and H with the appropriate side chain modifications as shown below.

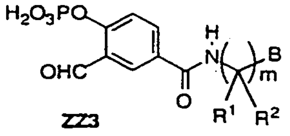


36 Compounds IA-IC



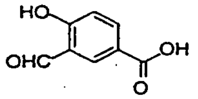
Compound	R^1	R^P	R^Q	MS
IA	$-CH_2CH_3$	$-CH_3$	$-(CH_2)_5CH_3$	495 (M-H)
IB	$-(CH_2)_2CO_2H$	$-CH_3$	$-(CH_2)_5CH_3$	539 (M-H)
IC	$-CH_2CH_3$	$-CH_2NH_2$	$-(CH_2)_5CH_3$	510 (M-H)

General Method J: Preparation of benzamides with aldehydes:

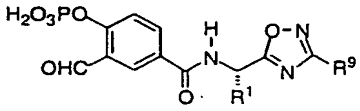


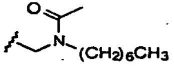
ZZ3

Compounds such as Compound ZZ3 (JA-JC below) can be prepared according to General Methods H and I with the appropriate substitution of the starting material as shown below.

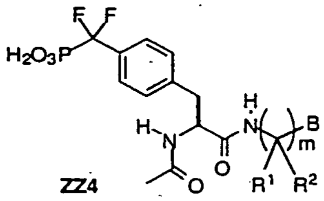


37. Compounds JA-JC



Compound	R^1	R^9	MS
JA	$-CH_2CH_3$	$-(CH_2)_2Ph$	458 (M-H)
JB	$-(CH_2)_2CO_2H$	$-(CH_2)_6CH_3$	496 (M-H)
JC	$-CH_2CH_3$		523 (M-H)

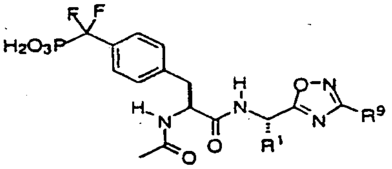
General Method JA: Preparation of difluorophosphonate derivatives:



ZZ4

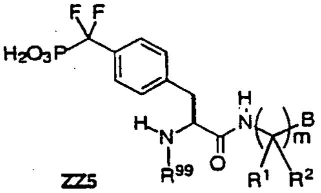
Compounds such as Compound ZZ4 (KA-KG below) can be prepared using Coupling Conditions C and D using the appropriate acid coupling partner along with the appropriate amine coupling partner. which can be prepared according to General Methods A. B. E, F and G. for example. The difluorophosphonate acid coupling partner can be prepared according to literature procedures (see for example Burke et al. *J. Org. Chem.* **1993**, *58*, 1336 and Smythe and Burke *Tetrahedron Lett.* **1994**, *35*, 551) and as described in WO 97/12903.

38. Compounds KA-KG



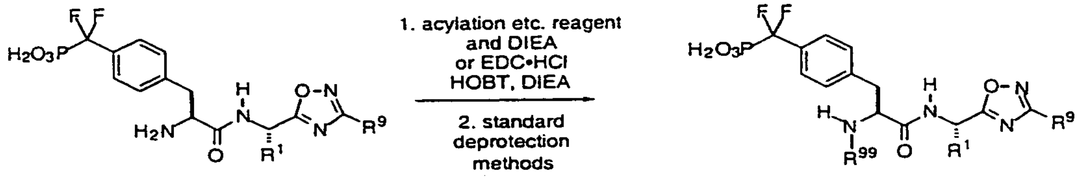
Compound	R1	R9	MS
KA	-CH2CH3	-$(CH_2)_5CH_3$	529 (M-H)
KB	-CH_2-(3-indole)	-$(CH_2)_5CH_3$	631 (M-H)
KC	-CH_3	-$CH_2(C_6H_4)$-4-CF_3	589 (M-H)
KD	-$(CH_2)_2CONH_2$	-$CH_2(C_6H_4)$-4-CF_3	646 (M-H)
KE	-CH_2OH	-$CH_2(C_6H_4)$-4-CF_3	605 (M-H)
KF	-CH_2OH	-$CH_2(C_6H_4)$-3,4-Cl_2	605 (M-H)
KG	-CH_3	-$CH_2(C_6H_4)$-3,4-Cl_2	589 (M-H)

General Method JB: Preparation of difluorophosphonate derivatives:

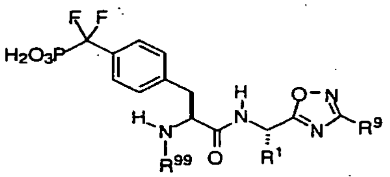


ZZ5

Compounds such as Compound ZZ5 (KM-KS below) with an NH substituent other than acetyl can be prepared according to Conditions C and D as shown in the scheme below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example, substituting the appropriate reagent (for example: acid, acid chloride, acid anhydride, sulfonyl chloride) and conditions. The difluorophosphonate acid coupling partner can be prepared according to literature procedures (see for example Burke et al. *J. Org. Chem*. **1993**, *58*, 1336 and Smythe and Burke *Tetrahedron Lett*. **1994**, *35*, 551) and as described in WO 97/12903. The free amine shown below is analogous to that which is acetylated in Coupling Conditions C.

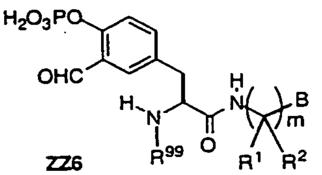

H2O3P
F F
H2N
H
N
O-N
N
R9
O
R1
1. acylation etc. reagent and DIEA or EDC•HCl HOBT, DIEA
2. standard deprotection methods
H
R99

38A. Compounds KM-KS

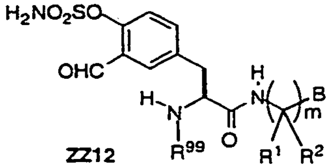


Cmpd	R99	R1	R9	MS
KM	-C(O)CH$_2$Ph	-CH2OH	-CH$_2$(C$_6$H$_4$)-4-CF$_3$	681 (M-H)
KN	-CO2CH$_2$Ph	-CH3	-CH$_2$(C$_6$H$_4$)-4-CF$_3$	665 (M-H)
KO	-CO2CH$_2$Ph	-CH2OH	-CH$_2$(C$_6$H$_4$)-3,4-Cl2	681 (M-H)
KP	-CO2CH$_2$Ph	-CH3	-CH$_2$(C$_6$H$_4$)-3,4-Cl2	665 (M-H)
KQ	-CO2CH$_2$Ph	-CH2OH	-CH$_2$-(2-naphthyl)	665 (M+H)
KR	-CO2CH$_2$Ph	-CH2OH	-CH$_2$(C$_6$H$_4$)-4-Cl	647 (M-H)
KS	-C(O)CH$_2$-(2-thienyl)	-CH2OH	-CH$_2$-(2-naphthyl)	671 (M+H)

General Method K: Preparation of aldehyde deriviatives related to pTyr:

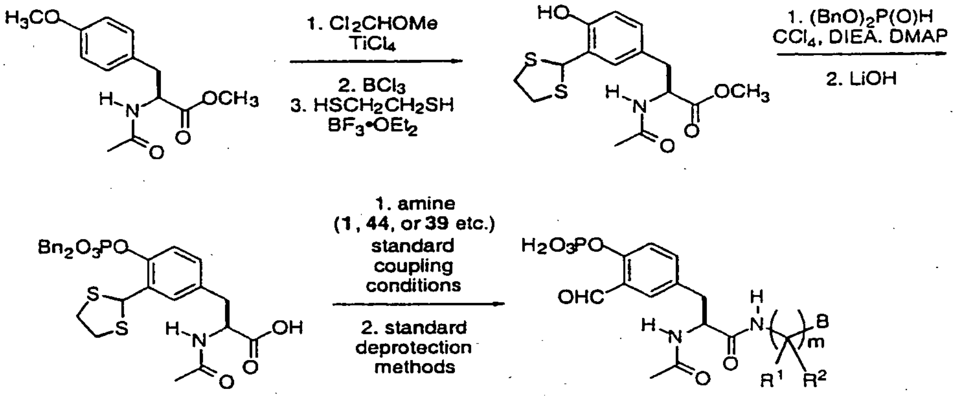


ZZ6

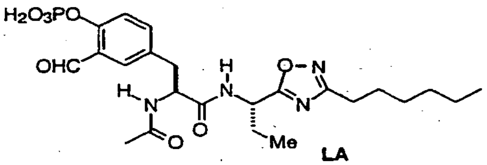


ZZ12

Compounds such as Compounds ZZ6 and ZZ12 can be prepared according to the general schemes shown below (for R^{99} = Ac), using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example, followed by standard deprotection methods.


H3CO
OCH3
H-N
1. Cl2CHOMe TiCl4
2. BCl3
3. HSCH2CH2SH BF3•OEt2
HO
S
S
OCH3
1. (BnO)2P(O)H CCl4, DIEA, DMAP
2. LiOH
Bn2O3PO
OH
1. amine (1, 44, or 39 etc.) standard coupling conditions
2. standard deprotection methods
H2O3PO
OHC
H
N
B
m
R1 R2

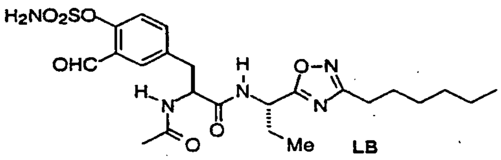
39. Compound LA



LA

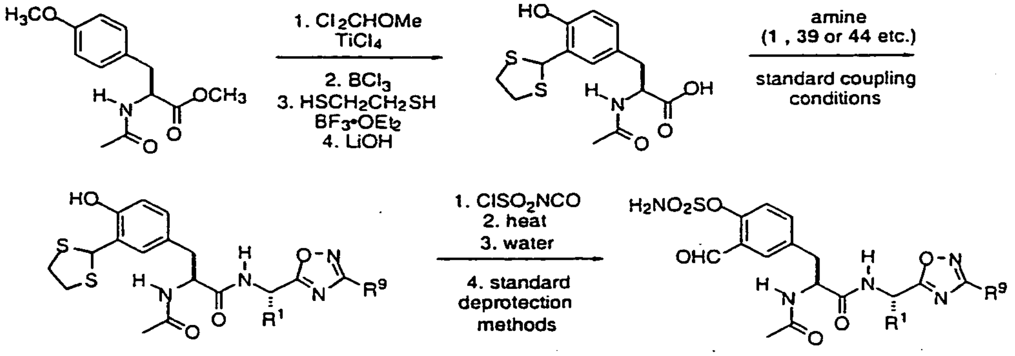
Compounds such as Compound LA can be prepared using General Methods F, G and K using the appropriate amine coupling partner. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 523 (M-H).

40. Compound LB

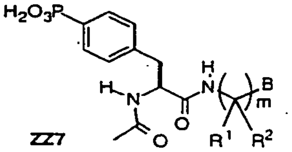


LB

Compounds such as Compound LB can be prepared using General Methods F, G and K using the appropriate amine coupling partner and the appropriate manipulations as shown in the scheme below. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 636 (M-H).



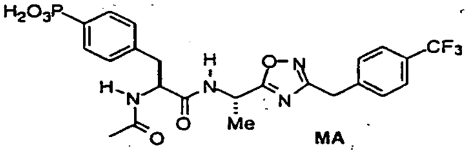
General Method L: Preparation of aryl phosphonates



ZZ7

Compounds such as Compound ZZ7 can be prepared according to Coupling Conditions C and D substituting the appropriate carboxylic acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. The carboxylic acid coupling partner can be prepared according to literature methods with the appropriate modifications. See for example: WO 97/12903; Stankovic et al. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1909; Petrakis et al. *J. Am. Chem. Soc.* **1987**, *109*, 2831.

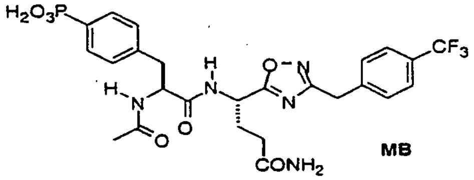
41. Compound MA



MA

Compounds such as Compound MA can be prepared according to General Method L. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 539 (M-H).

41A. Compound MB

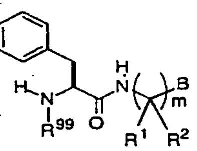


MB

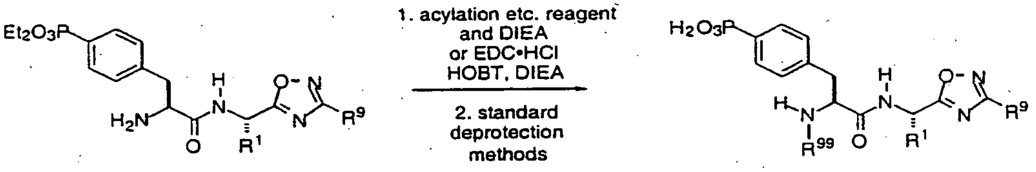
Compounds such as Compound MB can be prepared according to General Method L. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 596 (M-H).

General Method LA: Preparation of aryl phosphonates:

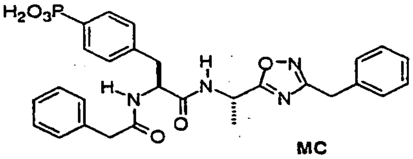
ZZ8



Compounds such as Compound ZZ8 with an NH substituent (R^{99}) other than acetyl can be prepared according to General Methods JB and L according to the general scheme shown below, substituting the appropriate reagent (for example: acid, acid chloride, acid anhydride, sulfonyl chloride) and conditions. The free amine shown below is analogous to that which is acetylated in Coupling Conditions C.


Et2O3P
H
N
O-N
N
R9
H2N
O
R1
1. acylation etc. reagent and DIEA or EDC•HCl HOBT, DIEA
2. standard deprotection methods
H2O3P
H
N
O-N
N
R9
H
N
R99
O
R1

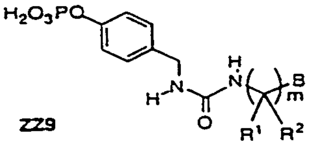
41B. Compound MC



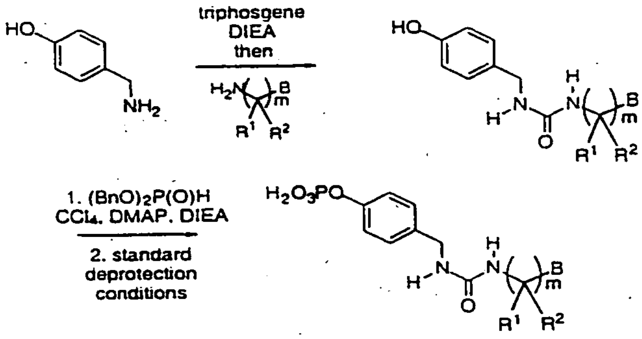
MC

Compounds such as Compound MC can be prepared according to General Method LA. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 547 (M-H).

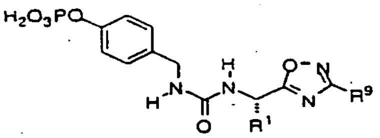
General Method M: Preparation of ureido analogs


ZZ9

Compounds such as Compound ZZ9 (NA-NC below) with a urea linkage similar to that shown above can be prepared according to the scheme below using the appropriate amine coupling partner. which can be prepared according to General Methods A. B. E. F and G. for example and according to literature methods. See for example: WO 97/12903: Plummer et al. *J. Med. Chem.* **1997**. *40*. 3719.

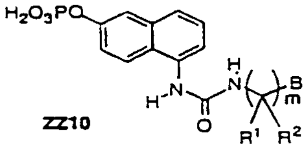


42. Compounds NA-NC

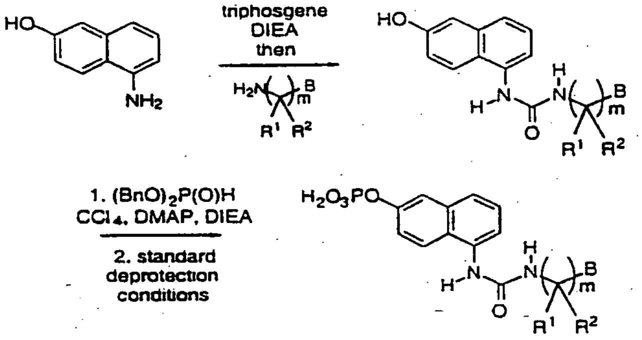


Compound	R1	R^9	MS
NA	$-CH_2$-(3-indole)	$-(CH_2)_5CH_3$	540 (M-H)
NB	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	499 (M-H)
NC	$-CH_2CH_3$	$-(CH_2)_5CH_3$	439 (M-H)

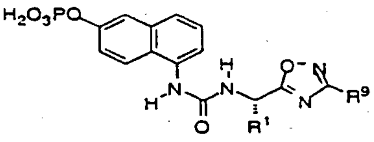
General Method MA: Preparation of naphthyl ureido analogs


ZZ10

Compounds such as Compound ZZ10 (NM-NQ below) with a urea linkage similar to that shown above can be prepared according to General Method M according to the scheme below and according to literature methods (see for example: WO 97/12903; Plummer et al. *J. Med. Chem.* **1997**, *40*, 3719), using the appropriate amine coupling partner. which can be prepared according to General Methods A, B, E, F and G, for example, and according to literature methods.

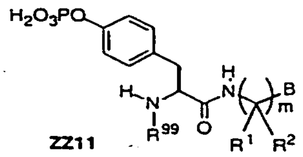


42. Compounds NM-NQ

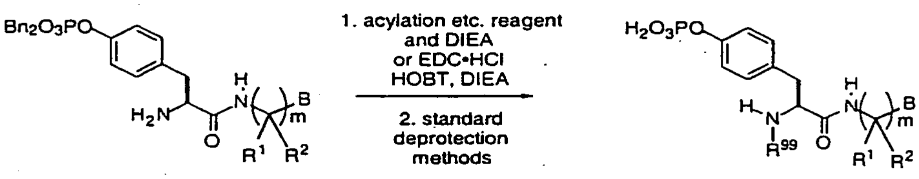


Compound	R^1	R^9	MS
NM	$-CH_3$	$-(CH_2)_5CH_3$	501 (M-H)
NO	$-CH_3$	$-CH_2(C_6H_4)$-3,4-Cl_2	535 (M-H)
NP	$-CH_2OH$	$-CH_2(C_6H_4)$-3,4-Cl_2	551 (M-H)
NQ	$-CH_2OH$	$-CH_2(C_6H_4)$-4-CF_3	551 (M-H)

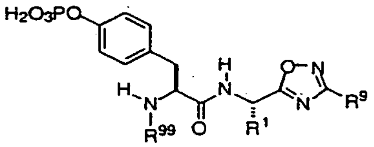
General Method N: Preparation of N-acyl or N-sulfonyl related analogs:


ZZ11

Compounds such as Compound ZZ11 with an NH substituent other than acetyl can be prepared according to Coupling Conditions C and D as shown in the scheme below, substituting the appropriate reagent (for example: acid, acid chloride, acid anhydride, sulfonyl chloride) and conditions. The free amine shown below is analogous to that which is acetylated in Coupling Conditions C.


1. acylation etc. reagent and DIEA or EDC•HCl HOBT, DIEA
2. standard deprotection methods

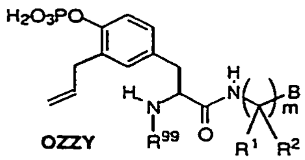
43. Compounds OA-OZM



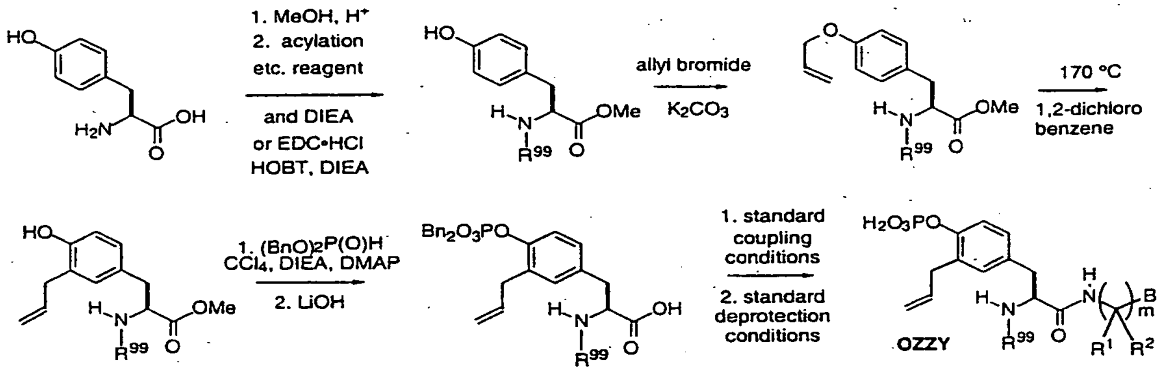
Cmpd	R^{99}	R^1	R^9	MS
OA	$-C(O)CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	632 (M-H)
OB	$-CO_2CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	648 (M-H)
OC	$-C(O)CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)$-4-Cl	598 (M-H)
OD	$-C(O)CH_2CN$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	580 (M-H)
OE	$-C(O)(CH_2)_3CO_2H$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	627 (M-H)
OF	$-C(O)(CH_2)_2CO_2H$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	613 (M-H)
OG	$-C(O)(CH_2)_2CO_2Et$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	642 (M-H)
OH	$-SO_2CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	667 (M-H)
OI	$-SO_2CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)$-4-Cl	634 (M-H)
OJ	$-SO_2CH_3$	$-CH_3$	$-CH_2(C_6H_4)$-4-Cl	558 (M-H)
OK	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)$-4-CF_3	647 (M-H)

OL	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)-3,4-Cl_2$	647 (M-H)
OM	$-C(O)CH_2Ph$	$-CH_2CO_2H$	$-CH_2(C_6H_4)-4-Cl$	642 (M-H)
ON	$-C(O)CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)-3,4-Cl_2$	632 (M-H)
OO	$-C(O)CH_2Ph$	-gem-Me_2	$-CH_2(C_6H_4)-4-CF_3$	647 (M+H)
OP	$-C(O)CH_2Ph$	$-CH_2CO_2H$	$-CH_2(C_6H_4)-4-CF_3$	677 (M+H)
OQ	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2$-(2-naphthyl)	631 (M+H)
OR	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)-4-Cl$	613 (M-H)
OS	$-C(O)CH_2$-(2-thienyl)	$-CH_2OH$	$-CH_2(C_6H_4)-4-CF_3$	637 (M-H)
OT	$-C(O)CH_2(C_6H_4)-3,4-F_2$	$-CH_3$	$-CH_2(C_6H_4)-4-CF_3$	667 (M-H)
OU	$-C(O)CH_2(C_6H_4)$-4-OMe	$-CH_3$	$-CH_2(C_6H_4)-4-CF_3$	661 (M-H)
OV	$-C(O)CH_2$-(3-indole)	$-CH_3$	$-CH_2(C_6H_4)-4-CF_3$	670 (M-H)
OW	$-C(O)CH_2$-(1-imidazole)	$-CH_3$	$-CH_2(C_6H_4)-4-CF_3$	621 (M-H)
OX	$-C(O)CH_2$-(2-naphthyl)	$-CH_3$	$-CH_2(C_6H_4)-4-CF_3$	681 (M-H)
OY	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)-4-F$	599 (M+H)
OZ	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)-3-CF_3$	649 (M+H)
OZA	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)-4-I$	705 (M-H)
OZB	$-C(O)CH_2$-(2-thienyl)	$-CH_2OH$	$-CH_2(C_6H_4)-4-I$	711 (M-H)
OZC	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)-4-Br$	657 (M-H)
OZD	$-C(O)CH_2Ph$	$-CH(OH)CH_3$	$-CH_2(C_6H_4)-4-CF_3$	663 (M+H)
OZE	$-C(O)CH_2Ph$	$-CH(OH)CH_3$	$-CH_2(C_6H_4)-3,4-Cl_2$	661 (M-H)
OZF	$-C(O)CH_2$-(2-thienyl)	$-CH_2OH$	$-CH_2$-(2-naphthyl)	636 (M+H)
OZG	$-C(O)CH_2Ph$	$-CH(OH)CH_3$	$-CH_2$-(2-naphthyl)	645 (M+H)
OZH	$-C(O)CH_2Ph$	$-CH(OH)CH_3$	$-CH_2(C_6H_4)-4-Br$	673 (M+H)
OZI	$-C(O)CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)$-4-(O-*n*-Pr)	622 (M-H)
OZJ	$-C(O)CH_2Ph$	-*i*-Bu	$-CH_2(C_6H_4)-3,4-Cl_2$	673 (M-H)
OZK	$-C(O)CH_2Ph$	-*i*-Bu	$-CH_2(C_6H_4)-4-CF_3$	673 (M-H)
OZL	$-C(O)CH_2Ph$	$-CH_3$	$-CH_2(C_6H_4)-4-Br$	641 (M-H)
OZM	$-C(O)CH_2Ph$	$-CH_3$	$-(CH_2)_3Ph$	591 (M-H)
OZN	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)$-3-Cl, 4-I	739 (M-H)

General Method NA: Preparation of ortho alkyl substituted phosphates:

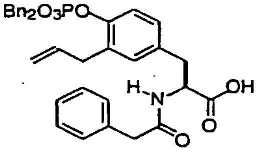

OZZY

Compounds such as Compound OZZY can be prepared according to the scheme shown below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Method N, for example.



1. MeOH, H+
2. acylation etc. reagent
and DIEA or EDC•HCl HOBT, DIEA
allyl bromide
K2CO3
170 °C
1,2-dichloro benzene
1. (BnO)2P(O)H CCl4, DIEA, DMAP
2. LiOH
1. standard coupling conditions
2. standard deprotection conditions
OZZY

Preparation of Acid 58

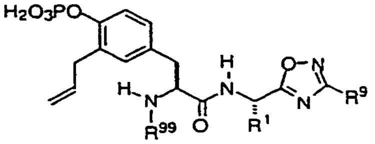

58

Commercially available L-tyrosine (5.0 g) was suspended in 100 mL of MeOH and HCl gas was bubbled through the reaction mixture for 10 min. The reaction mixture was stirred at rt for 45 min and then concentrated under reduced pressure. The resulting solid was dissolved in 20 mL of DMF and cooled to 0 °C. Phenylacetyl chloride (4.7 mL, 1.05 eq) was added, followed by DIEA (17.5 mL, 3 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min and then diluted with EtOAc and washed with 3 x 20 mL of H_2O, 2 x 20 mL of 10% aqueous citric acid, brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 5.2 g of the N-phenyl acetyl tyrosine methyl ester.

N-phenylacetyl tyrosine methyl ester was dissolved in 50 mL of anhydrous CH_3CN. Anhydrous potassium carbonate (4.6 g, 2 eq) was added, followed by allyl bromide (1.7 mL, 1.2 eq). The resulting reaction mixture was stirred at rt for 15 h. It was then quenched with H_2O and concentrated under reduced pressure. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. A portion of this material (2.0 g) was dissolved in 6 mL of 1,2-dichlorobenzene in a sealed tube. The reaction tube was purged with N_2 and sealed. It was then stirred at 170 °C for 2 days. Upon cooling to rt, the crude material was purified by chromatography (2:1 hexanes/EtOAc) to afford 526 mg of the desired ortho-allyl phenol derivative. This ortho-allyl phenol derivative (526 mg, 1.49 mmol) was dissolved in 15 mL of anhydrous CH_3CN and cooled to 0 °C. CCl_4 (0.720 mL, 5 eq) was added, followed by DIEA (0.545 mL, 2.1 eq) and a catalytic amount of DMAP (5 mg). After dibenzyl phosphite (0.480 mL, 1.5 eq) was added, the reaction mixture was stirred at 0 °C. After 45 min, the resulting reaction mixture was quenched with an aqueous solution of KH_2PO_4 (0.5 M). The volatile solvent was removed by concentration under reduced pressure, and the aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (1:1 hexanes/EtOAc) afforded 450 mg of the dibenzyl phosphate derivative. This material was dissolved in a 1:1 mixture of THF/H_2O and treated with 1 eq of LiOH at 0 °C. When all the starting material was consumed by TLC, the reaction mixture was quenched with dilute citric acid and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the corresponding acid.

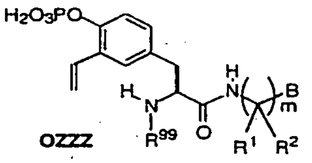
The above procedure could also be repeated using commercial N-acetyl tyrosine methyl ester instead of N-phenylacetyl tyrosine methyl ester in order to prepare the corresponding N-acetyl derivatives.

43A. Compounds OZZA-OZZD



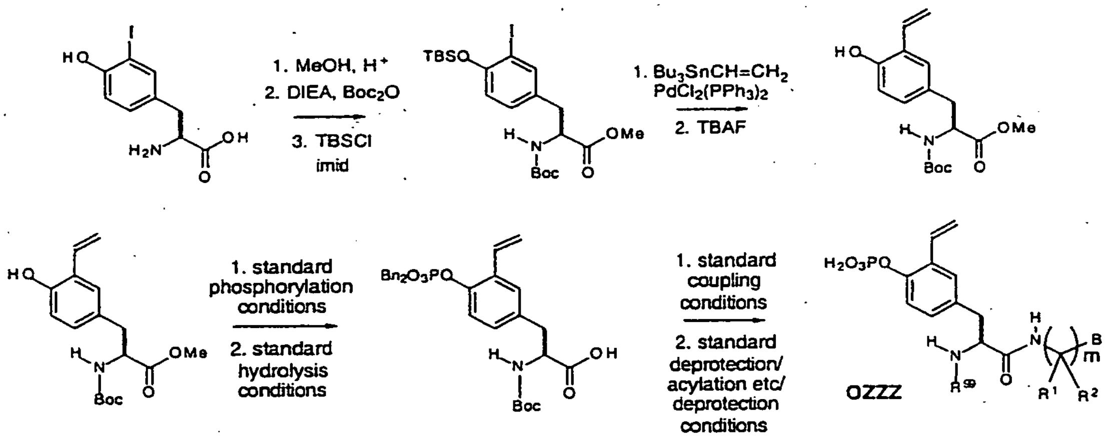
Cmpd	R^{99}	R^1	R^9	MS
OZZA	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2(C_6H_4)$-4-CF_3	669 (M-H)
OZZB	$-C(O)CH_3$	$-CH_3$	$-CH_2(C_6H_4)$-3,4-Cl_2	595 (M-H)
OZZC	$-C(O)CH_3$	$-CH_2OH$	$-CH_2(C_6H_4)$-4-CF_3	611 (M-H)
OZZD	$-C(O)CH_3$	$-CH_2OH$	$-CH_2$-(2-naphthyl)	593 (M-H)

General Method NB: Preparation of ortho alkyl substituted phosphates:

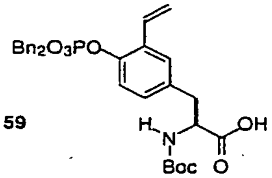


OZZZ

Compounds such as Compound OZZZ can be prepared according to General Method NA according to the scheme below using the appropriate acid coupling partner (**59**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Method N, for example.



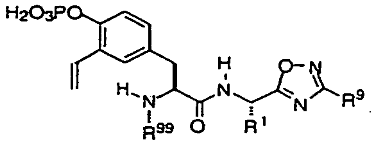
Preparation of Acid **59**



59

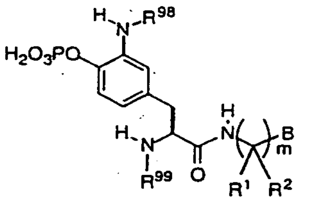
Commercially available 3-iodo-L-tyrosine (5.0 g) was suspended in 100 mL of MeOH and HCl gas was bubbled through the reaction mixture for 10 min. The reaction mixture was stirred at rt for 45 min and then concentrated under reduced pressure. The resulting solid was dissolved in 20 mL of DMF and cooled to 0 °C. Boc_2O (1.05 eq) was added, followed by DIEA (3 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min and then diluted with EtOAc and washed with 3 x 20 mL of H_2O, 2 x 20 mL of 10% aqueous citric acid and brine. The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure to affored the N-Boc 3-iodo-L-tyrosine methyl ester. A portion of this material (2.7 mmol) was dissolved in 15 mL of anhydrous DMF along with TBSCl (1.05 eq) and imidazole (1.05 eq). The reaction mixture was stirred at rt for 15 h. It was then diluted with EtOAc and washed with 3 x 10 mL of H_2O, brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (2:1 hexanes/EtOAc) afforded the fully protected 3-iodo-L tyrosine derivative. This material (1.55 mmmol) was dissolved in 8 mL of anhydrous DMF along with tributylvinyltin (2.33 mmol, 1.5 eq). Lithium chloride (3 eq) was added, followed by 2 mg of 2,6-di-tert-butyl-4-methylphenol and 54 mg of $PdCl_2(PPh_3)_2$ (0.05eq). The resulting reaction mixture was stirred at 80-85 °C for 1 h. It was then cooled to rt and diluted with EtOAc and washed with H_2O, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (2:1 hexanes/EtOAc) afforded 430 mg of the ortho-vinyl derivative. The TBS protecting group of this ortho-vinyl derivative was removed by dissolving 1 mmol of this material in 6 mL of anhydrous THF. TBAF was added as a 1 M solution in THF (1.2 eq) at rt and the reaction mixture was stirred at rt until all starting material was consumed, as determined by TLC. The reaction mixture was concentrated and purified by chromatography (1:1 hexanes/EtOAc) to afford the desired N-Boc-3-vinyl-L-tyrosine methyl ester. This material was subjected to the same reaction phosphorylation conditions as before to obtain the dibenzylphosphate derivative. Standard hydrolysis of the methyl ester was performed as described previously to afford the acid. This acid was subjected to the same reaction conditions (Coupling Conditions C and D) that were outlined previously in order to obtain the desired phosphates.

43B. Compound OZZG



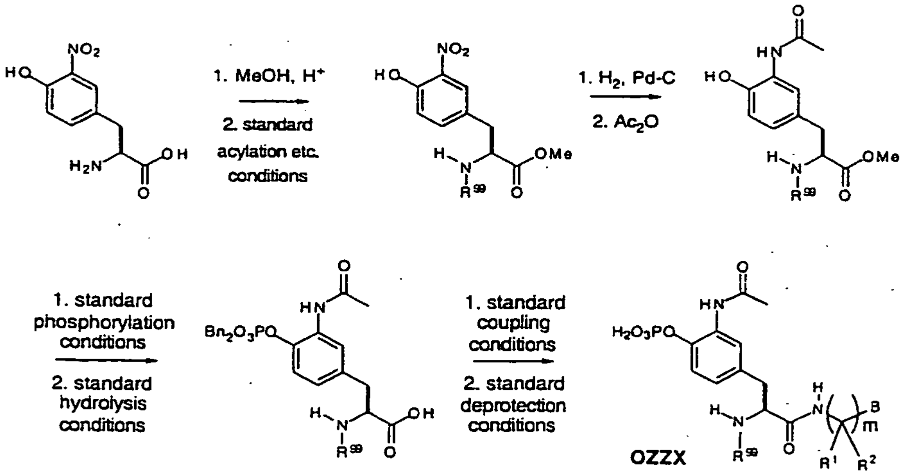
Cmpd	R^{99}	R^1	R^9	MS
OZZG	-C(O)CH_2Ph	-CH_2OH	-CH_2-(2-naphthyl)	655 (M-H)

General Method NC: Preparation of ortho amino substituted phosphates:



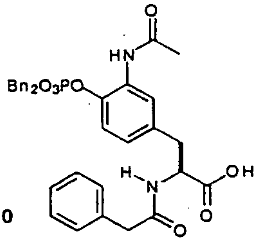
OZZX

Compounds such as Compound OZZX can be prepared as exemplified in the scheme shown below (with R^{98} = Ac) using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Method N, for example.



1. MeOH, H+
2. standard acylation etc. conditions
1. H2, Pd-C
2. Ac2O
1. standard phosphorylation conditions
2. standard hydrolysis conditions
1. standard coupling conditions
2. standard deprotection conditions
OZZX

Preparation of Acid **60**

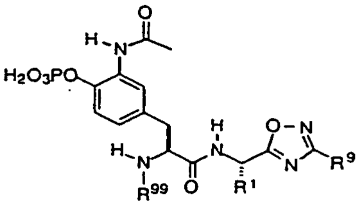


60

Commercially available 3-nitro-L-tyrosine (5.0 g, 0.02 mol) was suspended in 100 mL of MeOH, and HCl gas was bubbled through the reaction mixture for 10 min. The reaction mixture was stirred at rt for 45 min and then concentrated under reduced pressure. The resulting solid was dissolved in 20 mL of DMF and cooled to 0 °C. Phenylacetyl chloride (4.2 mL, 1.05 eq) was added, followed by DIEA (16 mL, 3 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min and then diluted with EtOAc and washed with 3 x 20 mL of H_2O, 2 x 20 mL of 10% aqueous citric acid, brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 6.5 g of the N-phenylacetyl 3-nitro-L-tyrosine methyl ester.

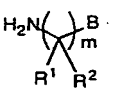
N-phenylacetyl 3-nitro-L-tyrosine methyl ester (1.0 g) was dissolved in 50 mL of MeOH. 10% Pd-C (100 mg) was then added, followed by 2 mL of concentrated HCl. The reaction mixture was hydrogenated at rt under 50 psi of H_2 for 15 h. It was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 mL of DMF along with Ac_2O (1.05 eq) and cooled to 0 °C. DIEA (3 eq) was then added and the resulting reaction mixture was stirred at 0 °C for 45 min. It was then diluted with EtOAc and washed with dilute citric acid, 3 x 20 mL of H_2O, brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by chromatography (1:1 EtOAc/hexanes) afforded 330 mg of the ortho-N-acetyl tyrosine methyl ester. Standard hydrolysis of the methyl ester was performed as described previously to afford the acid (**60**). This acid was subjected to the same reaction conditions (Coupling Conditions C and D) that were outlined previously in order to obtain the desired phosphates.

43C. Compounds OZZJ

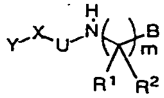


Cmpd	R^{99}	R^1	R^9	MS
OZZJ	$-C(O)CH_2Ph$	$-CH_2OH$	$-CH_2$-(2-naphthyl)	686 (M-H)

General Method ND: Preparation of additional heterocycle amines - General Methods O-U



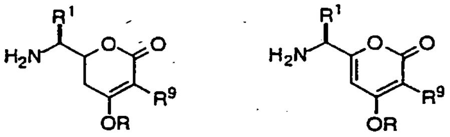
ZZ12



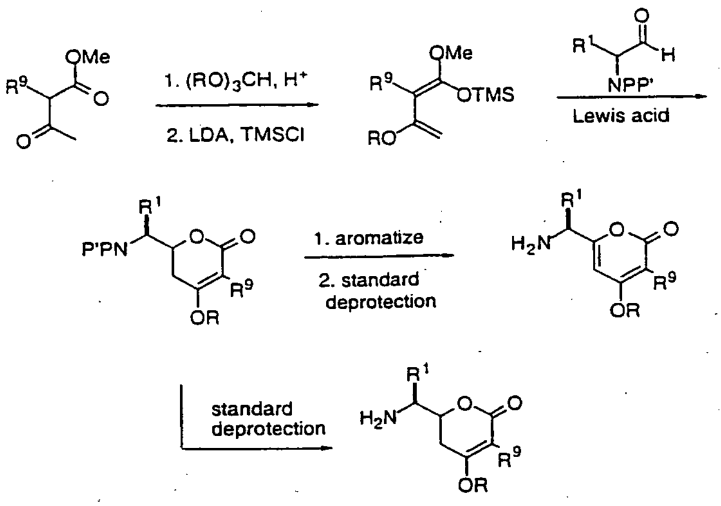
ZZ13

Compounds such as Compound ZZ13 prepared according to General Methods A-NC and V-ZT with representative heterocyclic amine tails such as ZZ12 as described within General Methods A-NC could also include many other heterocyclic amine tails, for example those described below in General Methods O-U with specific examples shown within General Methods S-TC, for example.

General Method O: Preparation of pyrones - hetero Diels Alder:

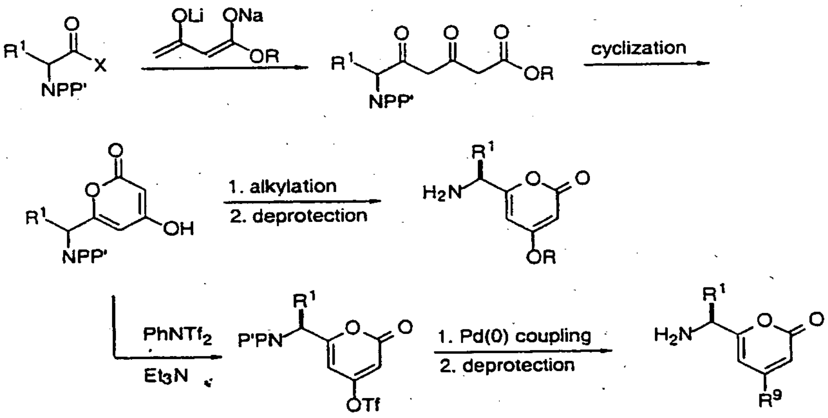


Many substituted pyrones can be prepared via the hetero Diels Alder reaction according to the method described in Midland et al. (*J. Am. Chem. Soc.* **1989**, *111*, 4368) according to the scheme shown below. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner.

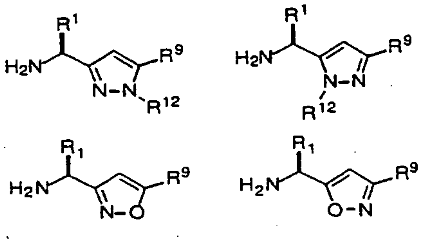


General Method P: Preparation of pyrones - cyclization:

Alternately, the pyrone can be prepared via a beta, gamma diketo ester with subsequent cyclization according to the method described in Hiyama et al. *Tetrahedron Lett.* **1988**, *29*, 6467 and Lygo *Tetrahedron* **1995**, *51*, 12859 as shown in the scheme below. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner.

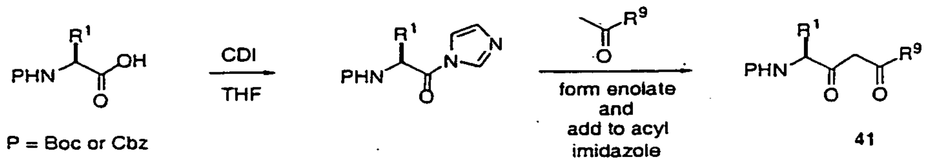


General Method Q: Preparation of pyrazoles and isoxazoles:

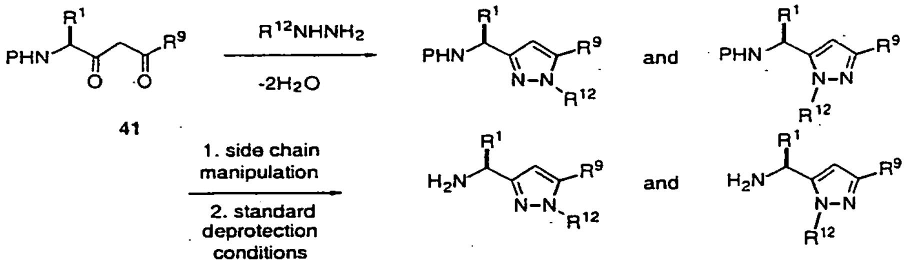


Many substituted pyrazoles and isoxazoles can be prepared according to the following schemes. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner.

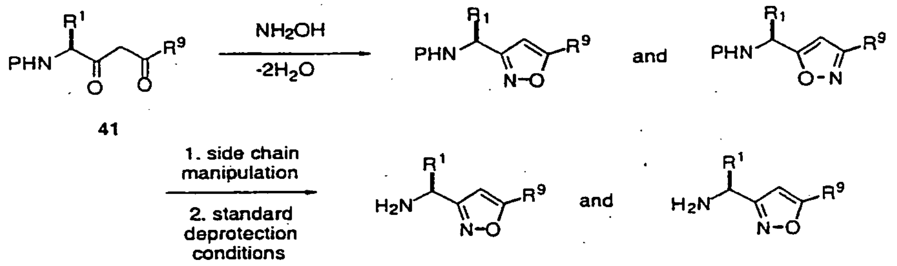
Preparation of diketone **41**:



Diketone **41** can then be used for pyrazole formation.

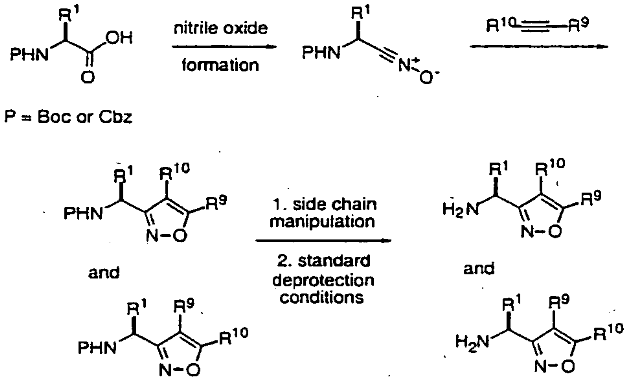

R1
PHN
R9
41
R12NHNH2
-2H2O
N-N
R12
and
1. side chain manipulation
2. standard deprotection conditions
H2N

Diketone **41** can also be used for isoxazole formation.


R1
PHN
R9
41
NH2OH
-2H2O
N-O
O-N
and
1. side chain manipulation
2. standard deprotection conditions
H2N

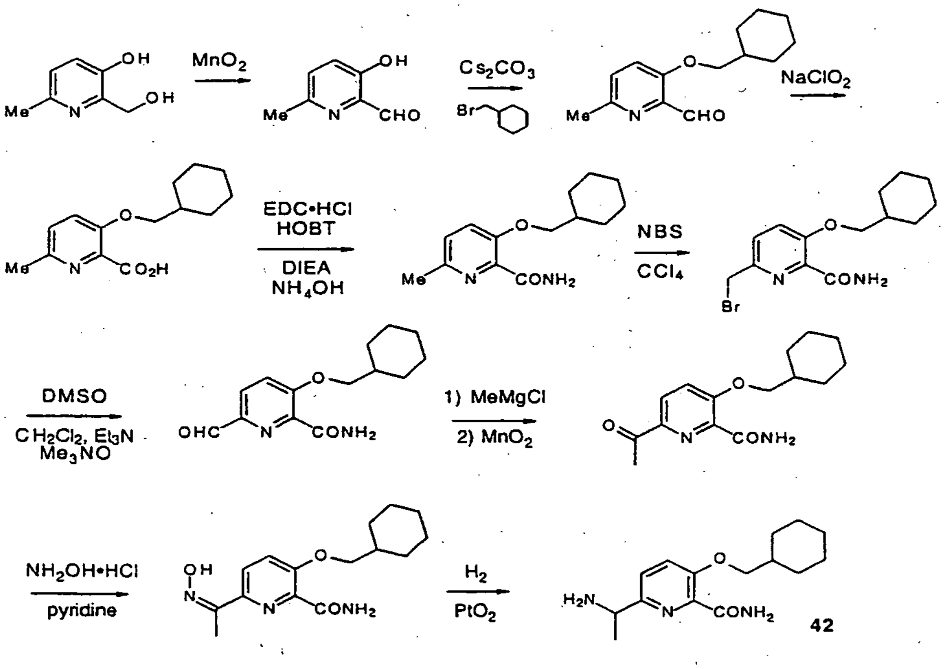
General Method R: Preparation of isoxazoles:

Alternately, the isoxazoles can be prepared according to the scheme shown below. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner.

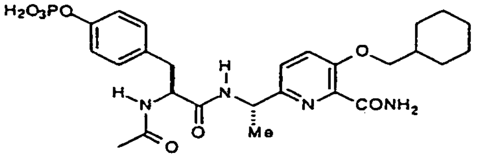

nitrile oxide
formation
P = Boc or Cbz
1. side chain manipulation
2. standard deprotection conditions
and
and

General Method S: Preparation of pyridines:

Many substituted pyridines can be prepared as exemplified by the scheme shown below for the preparation of Compound PA. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner. The starting diol allows for obvious side chain manipulations that can be used for the preparation of additional analogs.



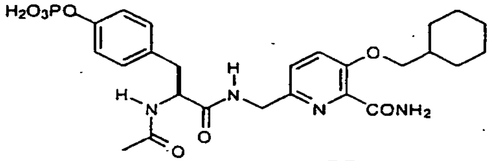
50. Compound PA



PA

Compounds such as Compound PA can be prepared from amine 42, prepared according to General Method S, using Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 675 (M-H).

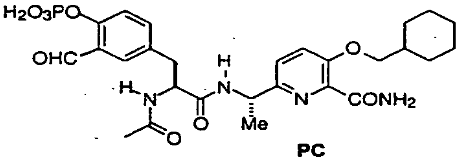
51. Compound PB



PB

Compounds such as Compound PB can be prepared from the appropriate amine, prepared according to General Method S (omitting the addition of the Grignard reagent), using Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 661 (M-H).

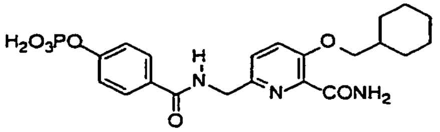
51A. Compound PC



PC

Compounds such as Compound PC can be prepared from amine 42, prepared according to General Method S, using General Method K. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 590 (M-H).

51B. Compound PD



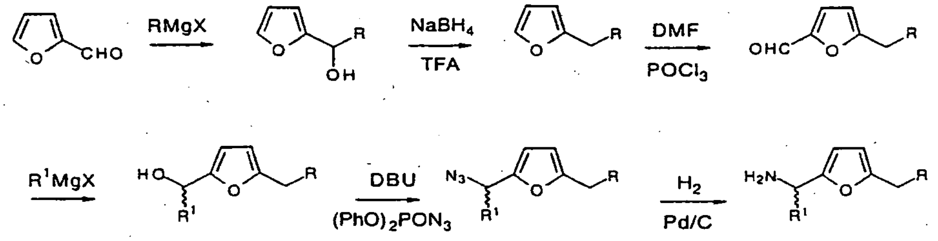
PD

Compounds such as Compound PD can be prepared from the appropriate amine, prepared according to General Method S (omitting the addition of the Grignard reagent), using

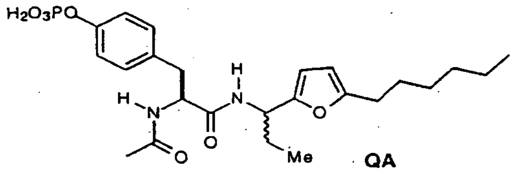
Coupling Conditions D and the carboxylic acid used in General Method H. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 462 (M-H).

General Method T: Preparation of furans:

Many substituted furans can be prepared as shown below in the following scheme. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner. Substitution of the 3 and/or 4 positions of the starting furan aldehyde allows for obvious side chain manipulations that can be used for the preparation of additional analogs.



52. Compound QA

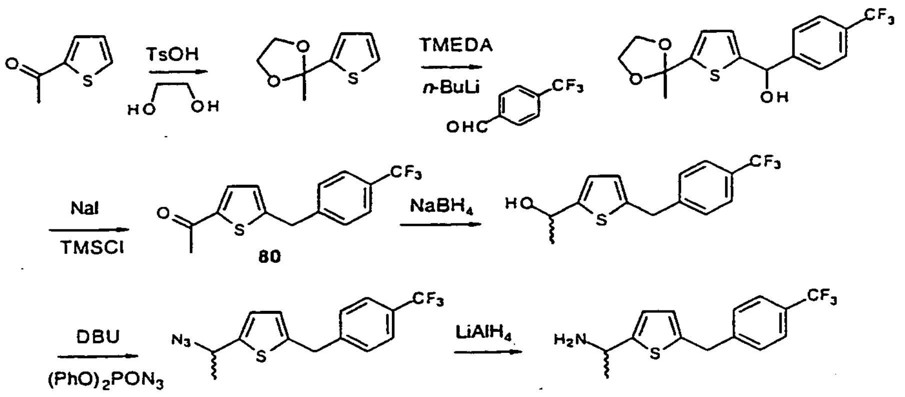


QA

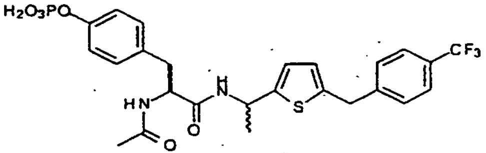
Compounds such as Compound QA can be prepared according to General Method T, substituting the appropriate Grignard reagents, followed by Coupling Conditions D. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 493 (M-H).

General Method TA: Preparation of thiophenes:

Many substituted thiophenes can be prepared as shown in the following scheme. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner. Substitution of the 3 and/or 4 positions of the starting thiophene allows for obvious side chain manipulations that can be used for the preparation of additional analogs.



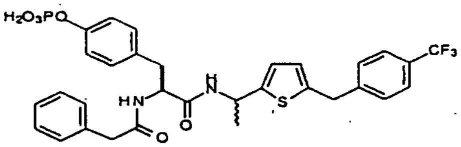
53. Compound QB



QB

Compounds such as Compound QB can be prepared according to General Method TA followed by Coupling Conditions D. Compound QB was isolated as a 1:1 mixture of diastereomers. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 569 (M-H).

53B. Compound QD

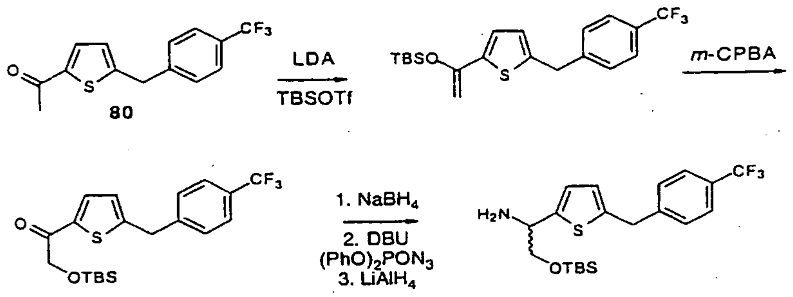


QD

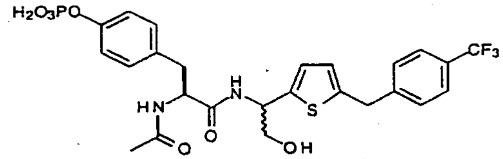
Compounds such as Compound QD can be prepared according to General Methods TA and N. Compound QD was isolated as a 1:1 mixture of diastereomers. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 645 (M-H).

General Method TB: Preparation of thiophenes:

Alternately, many substituted thiophenes can be prepared as shown below in the following scheme starting with ketone **80**, prepared in Method TA. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner. Substitution of the 3 and/or 4 positions of the starting thiophene allows for obvious side chain manipulations that can be used for the preparation of additional analogs.



54. Compound QC

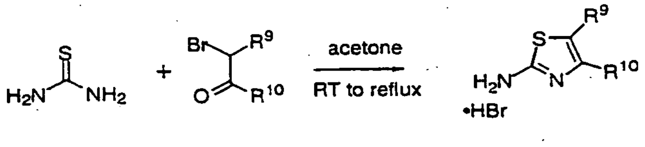


QC

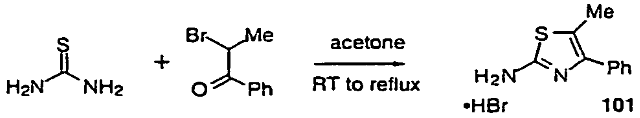
Compounds such as Compound QC can be prepared according to General Method TB followed by Coupling Conditions D. Compound QC was isolated as a 1:1 mixture of diastereomers. The two individual diastereomers could be separated by reverse-phase HPLC using a mixture of H_2O/CH_3CN with 0.1% TFA as the buffer. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 585 (M-H).

General Method TC: Preparation of aminothiazoles

Many substituted aminothiazoles can be prepared according to General Methods A and B, and as exemplified by the scheme shown below, substituting thiourea for the corresponding thioamide, as described in Patt, W. C. et al. *Synth. Commun.* **1990**, *20*, 3097 and Leanna, M. R. et al. *Tetrahedron Lett.* **1993**, *34*, 4485. The resulting amine or amine salt can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner.



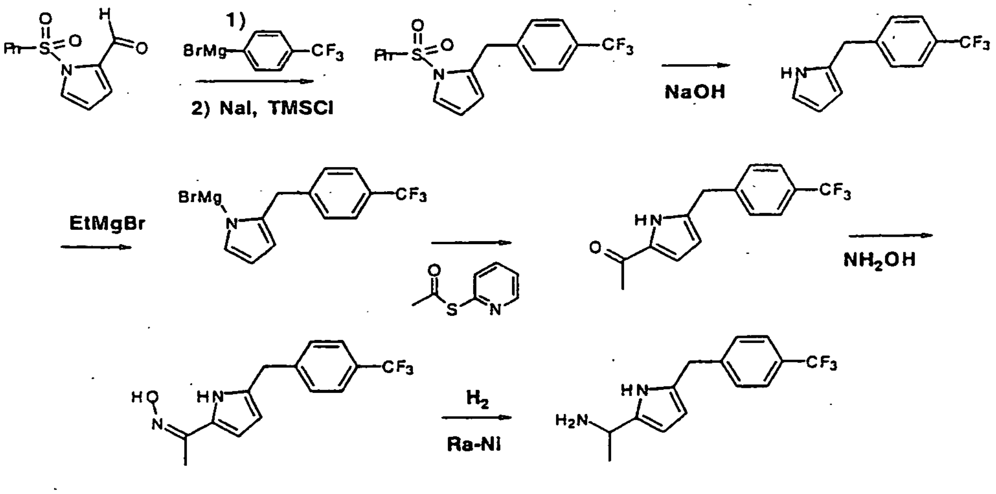
Preparation of amine salt **101**



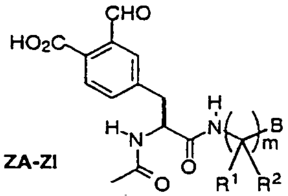
To a solution of 1.43 mL (9.39 mmol) of 2-bromopropiophenone (90% tech.) in 50 mL of acetone at RT was added 0.79 g (10.3 mmol) of thiourea. The resulting mixture was stirred at RT for 22 h. The white solid was isolated by filtration, rinsed several times with acetone, and dried in vacuo. MS and ^{1}H NMR indicated incomplete reaction. A portion (500 mg) of this solid was suspended in 10 mL of acetone and heated to mild reflux overnight. After cooling, the white solid was isolated by filtration, rinsed several times with acetone, and dried in vacuo. MS and ^{1}H NMR indicated that the reaction had gone to completion. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 191 (M+H).

General Method U: Preparation of pyrroles:

Many substituted pyrroles can be prepared as shown in the following scheme. The resulting amine can then be further elaborated according to Coupling Conditions C and D with the appropriate carboxylic acid coupling partner. Substitution of the 3 and/or 4 positions of the starting pyrrole allows for obvious side chain manipulations that can be used for the preparation of additional analogs.



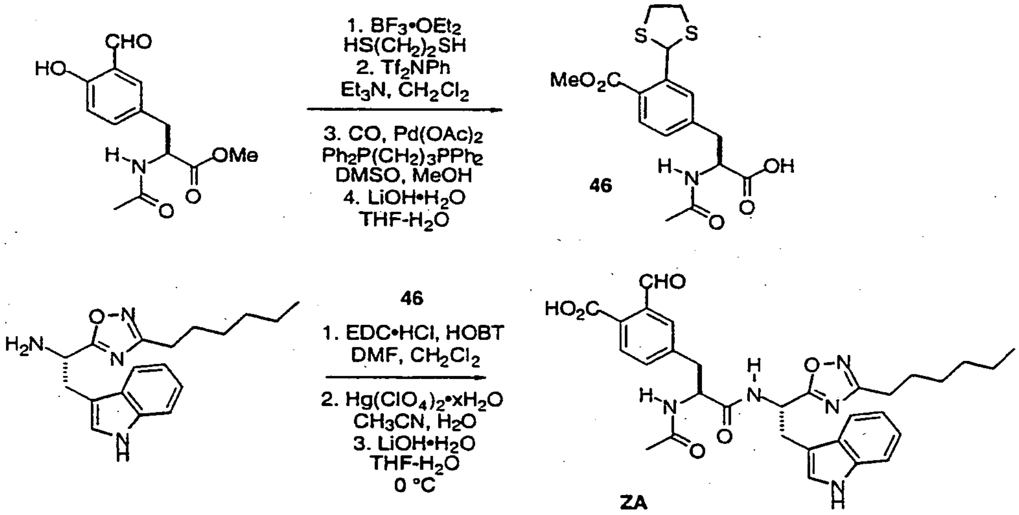
General Method V: Preparation of acid aldehydes:



ZA-ZI

Compounds such as Compounds ZA-ZI can be prepared according to the preparation of Compound ZA described below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies.

55. Compound ZA: (2-Formyl-4-{(S)-2-acetylamino-2-[(S)-1-carbamoyl-(5-hexyl-1,2,4-oxadiazol-3-yl)-2-(3-indolyl)ethyl]ethyl}benzoic acid)



(a) 3-(1,3-Dithiolan-2-yl)-N-acetyl-L-tyrosine methyl ester

To L-3-formyl-N-acetyltyrosine methyl ester (US patent 4,022,910) (0.13 g, 0.48 mmol) in methylene chloride (5 mL) at 0 °C was added boron trifluoride etherate (0.12 mL, 0.96 mmol) followed by ethanedithiol (0.044 mL, 0.53 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hour. The solution was poured into water and the layers separated. The aqueous layer was extracted with methylene chloride, and the combined extracts were washed with water, dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized from ethyl acetate/hexane (0.14 g, 82%). mp 97-99 °C.

(b) 3-(1,3-Dithiolan-2-yl)-4-(trifluoromethansulfonyloxy)-N-acetyl-L-phenylalanine methyl ester

To 3-(1,3-dithiolan-2-yl)-N-acetyltyrosine methyl ester (0.50 g, 1.46 mmol) and triethylamine (0.22 mL, 1.61 mmol) in methylene chloride (10 mL) at 0 °C was added N-phenyl-bis(trifluoromethanesulfonimide) (0.58 g, 1.61 mmol). The mixture was allowed to stir for five days then washed sequentially with 1 N NaOH, 1 N HCl, and brine. The organic layer was dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized from ethyl acetate/hexane (0.61 g, 87%). mp 116-118 °C.

(c) 3-(1,3-Dithiolan-2-yl)-4-(carboxymethyl)-N-acetyl-L-phenylalanine methyl ester

To 3-(1,3-dithiolan-2-yl)-4-(trifluoromethansulfonyloxy)-N-acetyl-L-phenylalanine methyl ester (0.51 g, 1.08 mmol) in DMSO/MeOH (3:2, 5 mL) was added triethylamine (0.33 mL, 2.36 mmol) followed by palladium acetate (0.0073 g, 0.033 mmol) and 1,3-bis(diphenylphosphino)propane (0.013 g, 0.034 mmol). Carbon monoxide was bubbled through for 3 min, and the mixture was heated to 80 °C for 24 hours. After cooling, the solution was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized from ethyl acetate/hexane (0.30 g, 72%). mp 113-119 °C.

(d) 3-(1,3-Dithiolan-2-yl)-4-(carboxymethly)-N-acetyl-L-phenylalanine (**46**)

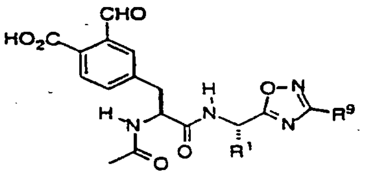
To the 3-(1,3-dithiolan-2-yl)-4-(carboxymethyl)-N-acetyl-L-phenylalanine methyl ester (0.22 g, 0.57 mmol) in THF (10 mL) at 0 °C was added lithium hydroxide (0.025 g, 0.60 mmol, 1 mL water). The mixture was stirred for 45 min., diluted with water, made acidic with 1 N HCl, and extracted with ethyl acetate. The combined extracts were washed with water. dried over magnesium sulfate and concentrated to a glassy solid which was homogeneous by RP HPLC (0.18 g, 86%). MS [M - H] 368.

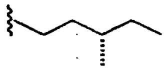
(e) 2-Formyl-4-{(S)-2-acetylamino-2-[(S)-1-carbamoyl-(5-hexyl-1,2,4-oxadiazol-3-yl)-2-(3-indolyl)ethyl]ethyl}benzoic acid (**ZA**)

3-(1,3-Dithiolan-2-yl)-4-(carboxymethyl)-N-acetyl-L-phenylalanine (**46**) (0.5 mmol) was dissolved in 2 mL of DMF and 5 mL of CH_2Cl_2 along with (S)-1-amino-1-(5-hexyl-1,2,4-

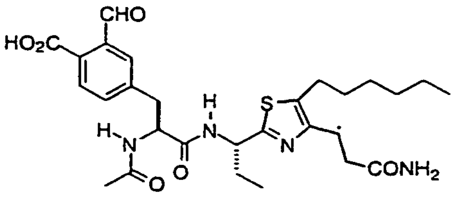
oxadiazol-3-yl)-2-(3-indolyl) ethane (0.6 mmol) (see general Method G). HOBT (0.6 mmol) and EDC (0.6 mmol) were added, followed by DIEA (0.75 mmol). The resulting reaction mixture was stirred at rt for 4 h. It was then concentrated, and the residue was taken up in EtOAc. The organic layer was washed with satd aq $NaHCO_3$, dilute aq citric acid, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting product was dissolved in 5 mL of CH_3CN. $Hg(ClO_4)_2$ was added dropwise at rt as a solution in 3 mL of water. The resulting reaction mixture was stirred at rt for 10 min and then filtered through a pad of Celite. The filtrate was concentrated. The residue was dissolved in 2 mL of THF and 0.5 mmol of LiOH was added as a solution in 2 mL of water at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. It was then acidified with 10% aq citric acid and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. A portion of the crude product was purified by reverse phase HPLC (H_2O/CH_3CN) to afford 6 mg of the desired product (**ZA**). Electrospray Mass Spectrum (50/50 MeCN/water) m/z 572 (M-H).

56. Compounds ZB-ZG



Compound	R^1	R^9	MS
ZB	$-(CH_2)_2CO_2H$	$-CH_2Chx$	527 (M-H)
ZC	$-(CH_2)_2CO_2H$	$-(CH_2)_6CH_3$	531 (M+H)
ZD	$-CH_2CH_3$	$-(CH_2)_5CH_3$	473 (M+H)
ZE	$-CH_2CH_3$	$-(CH_2)_6CH_3$	487 (M+H)
ZF	$-CH_3$	$-(CH_2)_5CH_3$	457 (M-H)
ZG	$-CH_2CH_3$		471 (M-H)

57. Compound ZH: (2-Formyl-4-{(S)-2-acetylamino-2-[(S)-1-carbamoyl-(5-hexyl-1,3-thiazol-2-yl)-2-(3-indolyl)ethyl]ethyl}benzoic acid)

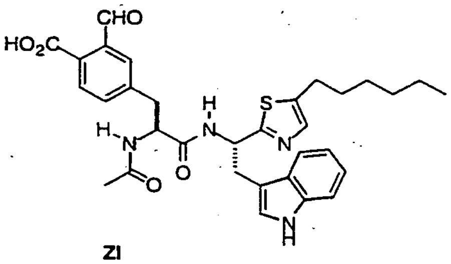


ZH

Compounds such as Compound ZH can be prepared according to General Method V, exemplified by the preparation of Compound ZA, substituting the appropriate amine coupling partner, which can be prepared according to General Method E. Flash chromatography (elution with 7:1 CH_2Cl_2-MeOH followed by 3:1 then 2:1 CH_2Cl_2-MeOH) gave 68.8 mg of a white solid: R_f 0.33 (3:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 MeCN/water + 0.1% formic acid) m/z 557 (M-H).

58. Compound ZI:

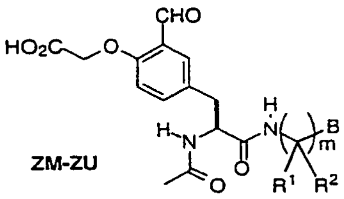
(2-Formyl-4-{(S)-2-acetylamino-2-[(S)-1-carbamoyl-(4-(3-(propionamide))(5-hexyl)-1,3-thiazol-2-yl)-2-(3-indolyl)ethyl]ethyl}benzoic acid)



ZI

Compounds such as Compound ZI can be prepared according to General Method V, exemplified by the preparation of Compound ZA, substituting the appropriate amine coupling partner which can be prepared according to General Method E. Compound ZI was purified by reverse phase preparative HPLC. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 589 (M+H).

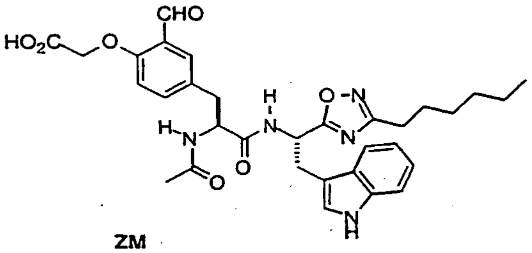
General Method W: Preparation of acetic acid aldehydes



ZM-ZU

Compounds such as Compounds ZM-ZU can be prepared according to the preparation of Compound ZM described below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Method V.

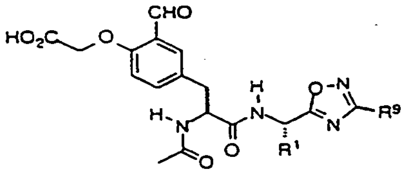
59. Compound ZM: (2-Formyl-4-{(S)-2-acetylamino-2-[(S)-1-carbamoyl-(5-hexyl-1,2,4-oxadiazol-3-yl)-2-(3-indolyl)ethyl]ethyl}phenoxyacetic acid

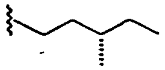


ZM

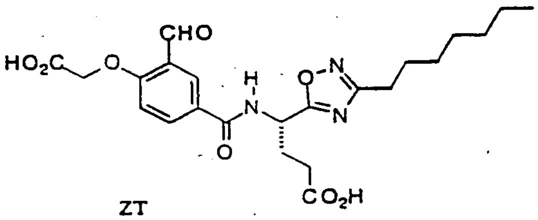
In a typical procedure, 3-(1,3-dithiolan-2-yl)-N-acetyl-L-tyrosine methyl ester (General Method V) was hydrolyzed to the corresponding acid using the standard procedure involving 2 equivalents of LiOH. The resulting acid (0.62 mmol) was dissolved in 2 mL of DMF and 5 mL of CH_2Cl_2 along with 0.62 mmol of (S)-1-amino-1-(5-hexyl-1,2,4-oxadiazol-3-yl)-2-(3-indolyl)ethane (prepared according to General Method G). HOBT (0.74 mmol) and EDC (0.74 mmol) were added, followed by DIEA (0.93 mmol). The resulting reaction mixture was stirred at rt for 4 h. It was then concentrated, and the residue was taken up in EtOAc. The organic layer was washed with sat $NaHCO_3$, dilute aq citric acid, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was dissolved in 5 mL of CH_3CN along with 1.86 mmol of *t*-butyl bromoacetate and 2.0 mmol of K_2CO_3. The resulting reaction mixture was stirred at rt for 2 days. It was then diluted with EtOAc and washed with brine, dried (Na_2SO_4) and concentrated. The resulting product was dissolved in 4 mL 25% TFA in CH_2Cl_2 and allowed to stand at rt for 1 h. It was then concentrated and dissolved in 4 mL of CH_3CN. $Hg(ClO_4)_2$ (1.10 mmol) was then added dropwise as a solution in 2 mL of water. The resulting reaction mixture was stirred at rt for 10 min and then filtered through a pad of Celite. The filtrate was concentrated & a portion was then purified by RP HPLC (H_2O/CH_3CN). MS (M-H) 602.

60. Compounds ZN-ZS



Compound	R^1	R^9	MS
ZN	$-(CH_2)_2CO_2H$	$-CH_2Chx$	559 (M+H)
ZO	$-CH_2$-(3-indole)		602 (M-H)
ZP	$-CH_2CH_3$	$-(CH_2)_4CH_3$	503 (M+H)
ZQ	$-CH_2CH_3$	$-(CH_2)_5CH_3$	558 (M+Na+H_2O)
ZR	$-(CH_2)_2CO_2H$	$-(CH_2)_6CH_3$	561 (M+H)
ZS	$-(CH_2)_2CO_2H$	$-(CH_2)_4CH_3$	533 (M+H)

61. Compound ZT: (S)-4-[3-formyl-4-carboxymethoxy-phenyl-carbonylamino]- 4-(5-heptyl-1,2,4-oxadiazol-3-yl)-butyric acid



ZT

(a) 3-(1,3-Dithiolan-2-yl)-4-hydroxybenzoic acid

This compound was prepared analogously to 3-(1,3-dithiolan-2-yl)-N-acetyl-L-tyrosine methyl ester (General Method V) using 3-formyl-4-hydroxybenzoic acid (Pfaltz & Bauer) to provide a solid. MS (M-H) 241.

(b) 3-(1,3-Dithiolan-2-yl)-4-hydroxyphenyl-carbonyl-L-Glu(OtBu)-OMe

This compound was prepared using the standard EDC/HOBT coupling conditions (as in Coupling Conditions C and D) with 3-(1,3-dithiolan-2-yl)-4-hydroxybenzoic acid and L-Glu(OtBu)-OMe to provide a white solid. MS (M-H) 440.

(c) 3-(1,3-Dithiolan-2-yl)-4-hydroxyphenyl-carbonyl-L-Glu(OtBu)-OH

This compound was prepared using the standard LiOH hydrolysis conditions to provide a solid. MS (M-H) 426.

(d) *t*-Butyl-(S)-4-[3-(1,3-dithiolan-2-yl)-4-hydroxy phenyl-carbonylamino]- 4-(5-heptyl-1,2,4-oxadiazol-3-yl)-butyrate

To 3-(1,3-dithiolan-2-yl)-4-hydroxypheny-carbonyl-L-Glu(OtBu)-OH (0.31 g, 0.72 mmol), HOBT (0.17 g, 0.87 mmol), EDC (0.13 g, 0.87 mmol), and n-heptamidoxime (0.11 g, 0.72 mmol) (prepared according to General Method F) was added 6.0 mL CH_2Cl_2/DMF (3:1) at 0 °C followed by DIEA (0.19 mL, 1.09 mmol). The resulting solution was stirred overnight at ambient temperature. The reaction mixture was diluted with EtOAc and washed successively with saturated $NaHCO_3$ and brine, dried over magnesium sulfate and concentrated. The crude material was dissolved in 2.5 mL of pyridine and heated at reflux for 30 min, diluted with EtOAc and washed successively with 10% aqueous citric acid and brine, dried over magnesium sulfate, concentrated and chromatographed over silica gel (1% MeOH/$CHCl_3$) to provide a white solid (0.13 g). MS (M-H) 548.

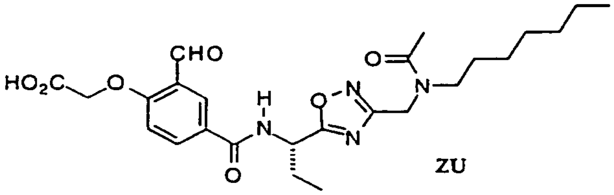
(e) *t*-Butyl-4-[(S)-3-(1,3-Dithiolan-2-yl)-4-carboxymethoxy-phenyl-carbonylamino]- 4-(5-heptyl-1,2,4-oxadiazol-3-yl)-butyrate

This compound was prepared using *t*-butyl-4-[(S)-3-(1,3-dithiolan-2-yl)-4-hydroxy -phenyl-carbonylamino]- 4-(5-heptyl-1,2,4-oxadiazol-3-yl)-butyrate and *t*-butylbromoacetate under standard alkylating (see General Method W) conditions to provide a solid. MS (M+H) 664.

(f) 4-[(S)-3-formyl-4-carboxymethoxy-phenyl-carbonylamino]- 4-(5-heptyl-1,2,4-oxadiazol-3-yl)-butyric acid

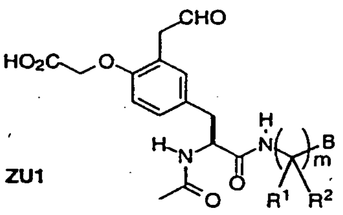
This compound was prepared using standard mercury perchlorate and TFA deprotection conditions (see General Methods V and W). Purification by reverse phase HPLC (CH_3CN/H_2O) provided a white solid. MS (M-H) 474.

61A. Compound ZU: 2-Formyl-4-{(S)-1-[5-(N-acetyl-N-heptyl-aminomethyl)-1,2,4-oxadiazol-3-yl]-propylcarbamoyl}-phenoxyacetic acid


ZU

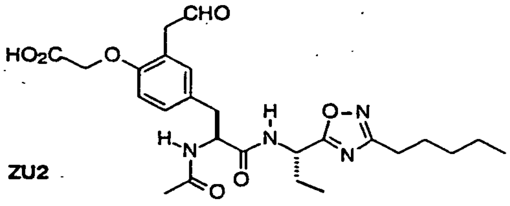
Compounds such as compound ZU can be prepared analogously to Compound ZT and according to General Method H using the appropriate oxime (N-acetyl-N-heptyloxime - prepared according to General Method I) and amino acid (L-Abu-OMe). Purification by reverse phase HPLC (CH_3CN/H_2O) provided a white solid. MS (M-H) 501.

General Method W1: Preparation of acetic acid acetic aldehydes


ZU1

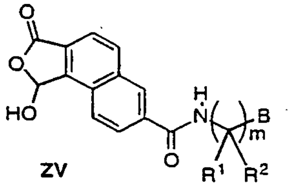
Compounds such as Compound ZU1 can be prepared according to General Methods W and NA, substituting obvious manipulations (ozonolysis of the allyl side chain and O-alkylation of the phenol) to install the appropriate acetic acid/aldehyde functional groups.

61B. Compound ZU2


ZU2

Compounds such as Compound ZU2 can be prepared according to General Method W1. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 503 (M+H).

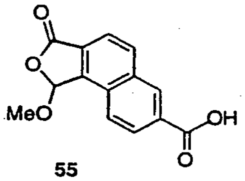
General Method WA: Preparation of naphthyl hydroxy furanones



ZV

Compounds such as Compound ZV can be prepared according to the preparation of Compound ZA described above using the appropriate acid coupling partner (55) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Methods V and K.

Preparation of Acid 55



55

(a) 5-Formyl-6-hydroxy-2-naphthoic acid

To a mixture of 941 mg (5.0 mmol) of 6-hydroxynaphthoic acid in 20 mL of $(CH_2Cl)_2$ at 0 °C under N_2 was added 1.0 mL (11.0 mmol) of $CHCl_2OMe$ followed by 1.15 mL (10.5 mmol) of $TiCl_4$ (added slowly). The mixture was stirred at rt overnight, then cooled to 0 °C and diluted with 25 mL of 10% aq HCl. The mixture was extracted with 3:1 EtOAc-THF and the extract washed with 25 mL of 1 *M* aq HCl. The first aqueous layer, which had suspended solids, was filtered and the pink solid washed with 1 *M* aq HCl. The solid was dried under high vacuum over P_2O_5 affording 197 mg. The filtrate was reextracted once with 3:1 EtOAc-THF and washed with the second aqueous layer. The combined extracts were concentrated *in vacuo* affording an additional 752 mg of about 90% purity. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) m/z 215 (M-H).

(b) Benzyl 5-formyl-6-hydroxy-2-naphthoate

To a suspension of 5-formyl-6-hydroxy-2-naphthoic acid (1.12 g, 5.18 mmol) in 7.3 mL DMF at rt under N_2 was added 569 mg (5.69 mmol) of K_2CO_3 and 1.11 mL (9.32 mmol) of benzyl bromide. The mixture was stirred for 3 days, at which point it was diluted with H_2O and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel, using 85:15 hexanes-EtOAc as the eluent, to give 410 mg (25%).

(c) Benzyl 5-formyl-6-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthoate

To a mixture of benzyl 5-formyl-6-hydroxy-2-naphthoate (410 mg, 1.33 mmol) in 6.25 mL of CH_2Cl_2 at rt under N_2 was added 0.28 mL (2.00 mmol) of Et_3N followed by 717 mg (2.00 mmol) of N-phenyl-bis(trifluoromethanesulfonimide). The mixture was stirred for 18 h at rt, diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel. Elution with 4:1 hexanes-Et_2O afforded 560 mg (96%).

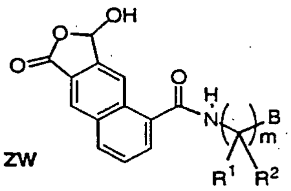
(d) 7-Benzyloxycarbonyl-1-methoxynaphtho[1,2-*c*]furan-3(1*H*)-one

To a solution of benzyl 5-formyl-6-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthoate 560 mg (1.27 mmol) in 3.6 mL dry of DMSO and 2.54 mL of dry MeOH at rt was added 0.39 mL (2.8 mmol) of Et_3N, 8.5 mg (0.038 mmol) of $Pd(OAc)_2$, and 15.6 mg (0.038 mmol) of dppp. The mixture stirred under an atmosphere of CO (balloon) at rt for 1.5 h and then at 60 °C for 2 h. The mixture was then cooled to rt, diluted with H_2O and extracted with EtOAc followed by $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel. Elution with 85:15 hexanes-EtOAc afforded a mixture of products. The mixture was diluted with Et_2O, washed with 10 mL of 1.0 *M* aqueous NaOH, H_2O and saturated aqueous NH_4Cl. The organic extract was dried over $MgSO_4$ and concentrated *in vacuo* affording 33 mg (10%).

(e) 7-Hydroxycarbonyl-1-methoxynaphtho[1,2-*c*]furan-3(1*H*)-one (55)

A mixture of 7-benzyloxycarbonyl-1-methoxynaphtho[1,2-*c*]furan-3(1*H*)-one (33 mg, 0.095 mmol) and a catalytic amount of 10% Pd/C in 2 mL of EtOH was stirred at rt under an atmosphere of H_2 (balloon) for 2 h. The mixture was then diluted with THF and filtered through a pad of Celite. The filtrate was then concentrated *in vacuo*. The crude material was dissolved in saturated aqueous $NaHCO_3$ and washed with EtOAc. The aqueous layer was then acidified with 1 *M* aqueous HCl and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated *in vacuo* affording 19 mg (79%).

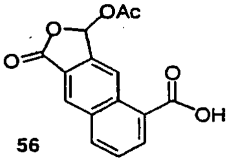
General Method WB: Preparation of naphthyl hydroxy furanones



ZW

Compounds such as Compound ZW can be prepared according to the preparation of Compound ZA described above using the appropriate acid coupling partner (**56**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Methods V and K.

Preparation of Acid **56**



56

(a) Methyl 3,5-Dihydroxy-2-naphthoate

To a solution of 3,5-dihydroxy-2-naphthoic acid (5.05 g) in MeOH (100 mL) was added TsOH (93 mg). The reaction mixture was stirred at reflux for 18 hours and then $CH(OMe)_3$ (1 mL) was added. The reaction mixture was stirred at reflux for an additional 5 hours, at which point H_2SO_4 (10 drops) was added. After an additional 18 h, the reaction mixture was cooled to rt, poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as a yellow-white solid (5.19 g, 96%).

(b) Methyl 3,5-Bis[[(trifluoromethyl)sulfonyl]oxy]-2-naphthoate

To a solution of methyl 3,5-dihydroxy-2-naphthoate (2.0 g, 9.17 mmol) in CH_2Cl_2 (43 mL) at rt was added Et_3N (4.0 g, 5.6 mL, 40.3 mmol) followed by $PhNTf_2$ (7.2 g, 20.2 mmol). The solution was then stirred at rt for 18 hours. The reaction mixture was diluted with Et_2O and washed with 1.0 *M* aqueous HCl. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was chromatographed on silica gel (20:1 hexanes:EtOAc) to give a 1:1 mixture of the title compound and PhNHTf.

(c) Methyl 3,5-Diethenyl-2-naphthoate

To a solution of a 1:1 mixture of methyl 3,5-bis[[(trifluoromethyl)sulfonyl]oxy]-2-naphthoate and PhNHTf (3.24g, 4.5 mmol) in DMF (11.25 mL) was added $(PPh_3)_2PdCl_2$ (158 mg, 0.23 mmol) and LiCl (1.14 g, 27.0 mmol). The mixture was stirred at rt for 20 min at which point $Bu_3SnCH=CH_2$ (2.6 mL, 9.45 mmol) was added. The reaction mixture was heated for 90 min whereupon saturated aqueous KF was added. The resulting precipitate was removed by filtration and the filtrate extracted with EtOAc. The organic layer was washed with 1.0 *M* aqueous HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was chromatographed on silica gel (2% to 5% EtOAc/hexanes) to give the title compound (slightly impure as judged by ^{1}H-NMR) as a clear oil. This material was used in the next reaction without further purification.

(d) Methyl 3,5-diformyl-2-naphthoate

O_3 was bubbled through a solution of slightly impure methyl 3,5-diethenyl-2-naphthoate (from the previous reaction) in CH_2Cl_2 (30 mL) and pyridine (2 mL) at -78 °C until a blue color persisted. Next, Me_2S (2 mL) was added, producing a yellow color. The mixture warmed to rt over 18 h. All volatiles were then removed *in vacuo*. The crude material was chromatographed on silica gel (20:1 to 85:15 hexanes:EtOAc) to give the title compound (slightly impure as judged by ^{1}H-NMR). The material was used in the next step without further purification.

(e) 5-Formyl-3-hydroxynaphtho[2,3-*c*]furan-1(3*H*)-one

To a solution of the impure methyl 3,5-diformyl-2-naphthoate in THF (10 mL) at rt was added 1.0 *M* aqueous LiOH (5 mL, 5 mmol). After 1.5 hours, the reaction mixture was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified with 1.0 *M* aqueous HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (200 mg, 19% from methyl 3,5-diethenyl-2-naphthoate) as a white solid.

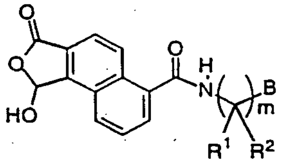
(f) 3-Acetoxy-5-formylnaphtho[2,3-*c*]furan-1(3*H*)-one

To a solution of 5-formyl-3-hydroxynaphtho[2,3-*c*]furan-1(3*H*)-one (190 mg, 0.83 mmol) in pyridine (1.66 mL) at rt was added Ac_2O (126 mg, 0.117 mL, 1.25 mmol). The solution was stirred at rt for 18 hours and then poured into brine and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The crude material was chromatographed on silica gel (3:1 hexanes:EtOAc) to give the title compound (100 mg, 44%).

(g) 3-Acetoxy-5-hydroxycarbonylnaphtho[2,3-*c*]furan-1(3*H*)-one (**56**)

To a solution of 3-acetoxy-5-formylnaphtho[2,3-*c*]furan-1(3*H*)-one (100 mg, 0.377 mmol) in MeCN (0.373 mL) and H_2O (0.150 mL) at rt was added NaH_2PO_4 (15.3 mg, 0.097 mmol) followed by 50% H_2O_2 (0.026 mL). $NaClO_2$ (1.0 *M* in H_2O, 0.518 mL) was added over the course of 2 h via syringe pump. The reaction mixture was then diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give the title compound **56** (87 mg, 80%).

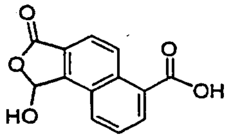
General Method WC: Preparation of naphthyl hydroxy furanones



ZX

Compounds such as Compound ZX can be prepared according to the preparation of Compound ZA described above using the appropriate acid coupling partner (**57**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies and is similar to General Methods V and K.

Preparation of Acid **57**



57

(a) 5-Formyl-6-hydroxy-1-naphthoic acid

To a solution of 6-hydroxy-1-naphthoic acid (5.0 g, 37.6 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added 1.0 M $TiCl_4$ in CH_2Cl_2 (80 mL, 80 mmol) dropwise. After 5 min, Cl_2CHOCH_3 (10.16 g, 88.4 mmol, 8 mL) was added. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C and quenched with 100 mL H_2O, followed by 100 mL 1.0 *M* aqueous HCl. The resulting mixture was filtered, and the remaining solid was dissolved in 100 mL 1.0 *M* aqueous NaOH and filtered. The basic filtrate was acidified with 1.0 *M* aqueous HCl, and the resulting red solid was filtered and washed with 1.0 *M* aqueous HCl and Et_2O to give the title compound.

(b) Methyl 5-formyl-6-hydroxy-1-naphthoate

To a solution of 5-formyl-6-hydroxy-1-naphthoic acid (1.89 g, 8.75 mmol) in THF (200 mL) and EtOH (200 mL) was slowly added CH_2N_2 in Et_2O until no SM remained by HPLC. The excess CH_2N_2 was quenched with a small amount of AcOH, and the volatiles were then removed *in vacuo*. The resulting crude material was chromatographed on silica gel (85:15 hexanes:EtOAc) to give the title compound.

(c) Methyl 5-formyl-6-[(trifluoromethyl)sulfonyl]oxy-1-naphthoate

To a solution of methyl 5-formyl-6-hydroxy-1-naphthoate (500 mg, 2.17 mmol) in CH_2Cl_2 (10.2 mL) at rt was added Et_3N (483 mg, 4.78 mmol, 0.664 mL) followed by $PhNTf_2$ (928 mg, 2.6 mmol). The mixture was stirred for 18 h and then diluted with Et_2O and washed with 1.0 M HCl. The extract was dried with $MgSO_4$ and concentrated *in vacuo*. The crude material was chromatographed on silica gel (20:1 hexanes/EtOAc), and the material thus obtained was recrystallized from hexanes to give 1.0 g of a 3:2 mixture of the title compound and PhNHTf (~90% yield).

(d) 1-Methoxy-6-methoxycarbonylnaphtho[1,2-*c*]furan-3(1*H*)-one

To a solution of a 3:2 mixture of methyl 5-formyl-6-[(trifluoromethyl)sulfonyl]oxy-1-naphthoate (1.5 mmol) and PhNHTf in DMSO (4.5 mL) at rt was added $Pd_2(dba)_3{\bullet}CHCl_3$ (155 mg, 0.217 mmol), and MeOH (4.34 mL). CO gas was bubbled through the mixture for 3 min and then Et_3N (0.522 mL, 3.75 mmol) was added. The mixture was then heated to 60 °C. CO gas was bubbled through the mixture for another 10 min, and the mixture was stirred for an additional 30 min. The mixture was then poured into 1.0 *M* aqueous HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was chromatographed on silica gel (20:1 hexanes:EtOAc) to give the title compound.

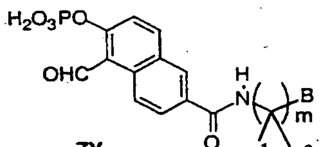
(e) 1-Hydroxy-6-hydroxycarbonylnaphtho[1,2-*c*]furan-3(1*H*)-one

To a solution of 1-methoxy-6-methoxycarbonylnaphtho[1,2-*c*]furan-3(1*H*)-one (160 mg, 0.588 mmol) in THF (10 mL) at rt was added 1.0 *M* aqueous LiOH (2 mL, 2 mmol). The mixture was stirred for 2 h, acidified with 1.0 *M* HCl and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting material was carried into next reaction.

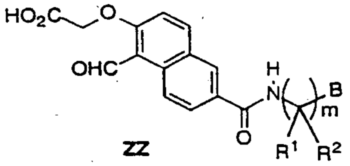
(f) 6-Hydroxycarbonyl-1-methoxycarbonylnaphtho[1,2-*c*]furan-3(1*H*)-one (**57**)

To a solution of 1-hydroxy-6-hydroxycarbonylnaphtho[1,2-*c*]furan-3(1*H*)-one in dry MeOH (15 mL) was added TsOH (150 mg) and $CH(OMe)_3$ (0.5 mL). The mixture was stirred at reflux for 2 h. The mixture was then cooled to rt, diluted with saturated aqueous $NaHCO_3$, acidified with AcOH and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was chromatographed on silica gel (85:15:1 to 66:33:1 hexanes:EtOAc:AcOH) to give the title compound (**57**) (120 mg, 79% from (d)).

General Method WD: Preparation of naphthyl aldehydes

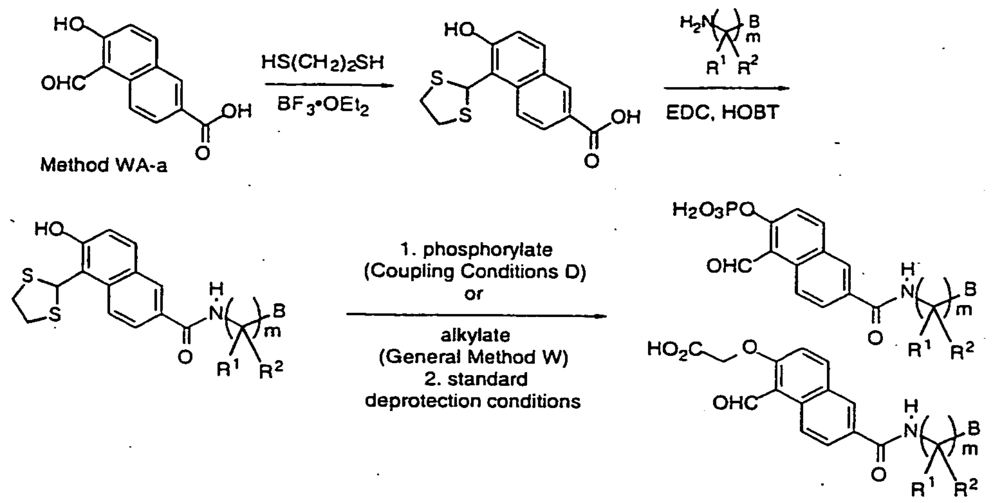


ZY



ZZ

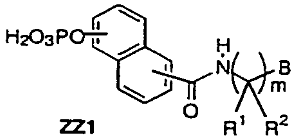
Compounds such as Compounds ZY and ZZ can be prepared according to the scheme below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies and is similar to General Methods V and K.



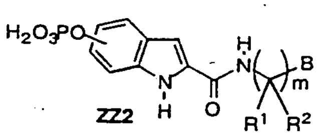
ZY

ZZ

General Method WD1: Preparation of naphthyl and indole phosphates



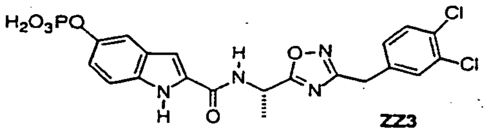
ZZ1



ZZ2

Compounds such as ZZ1 and ZZ2 can be prepared according to General Method WD substituting the appropriate hydroxy acid starting material.

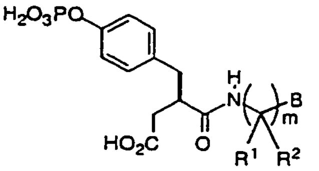
62. Compound ZZ3



ZZ3

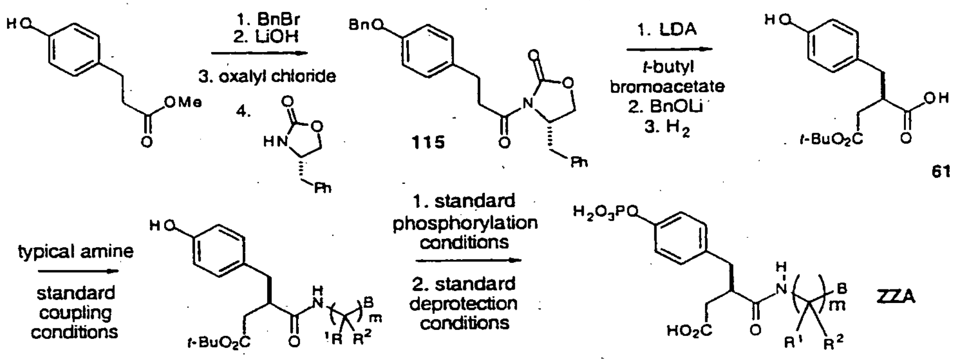
Compounds such as Compound ZZ3 can be prepared according to General Method ZA. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 508 (M-H).

General Method WE: Preparation of succinic acid derivatives

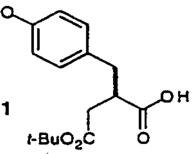


ZZA

Compounds such as Compounds ZZA can be prepared according to the scheme below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies and is similar to General Method WD.



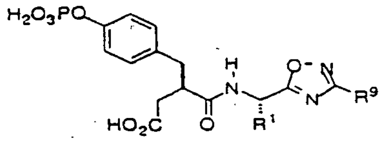
Preparation of Acid **61**


61

In a typical procedure, methyl 3-(4-hydroxyphenyl)propionate (0.05 mol) was dissolved in 100 mL of methyl ethyl ketone along with BnBr (1.05 eq) and DIEA (2 eq). The reaction mixture was stirred at reflux until all starting material was consumed, as observed by TLC (2 days). It was then quenched with H_2O and concentrated under reduced pressure. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 13.50 g of the benzylated product. This material was dissolved 100 mL of THF and LiOH (1.1 eq) was added as a solution in 100 mL of H_2O at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. It was then concentrated to remove all the volative solvent and acidified to pH 2 with 3 N HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford the acid. This material (12.70 g, 49.6 mmol) was suspended in 150 mL of CH_2Cl_2, and oxalyl chloride was added (2 eq). After a catalytic amount of DMF (0.050 mL) was added, the reaction mixture was stirred at rt for 3 h. It was then concentrated under reduced pressure and dried under high vacuum to afford to acid chloride. In a separate, oven-dried flask, 8.8 g of (S)-(-)-(4)-benzyl-2-oxazolidinone (Aldrich) was dissolved in 300 mL of anhydrous THF and cooled to -78 °C. *n*-BuLi (1 eq, 2.5 M solution in hexanes) was added slowly at -78 °C over a period of about 10 min. The reaction mixture was stirred at -78 °C for 20 min, and the freshly prepared 3-(4-benzyloxyphenyl)propionyl chloride was added as a solution in 200 mL of anhydrous THF. The reaction mixture was warmed to rt and stirred for 1 h. It was then quenched with brine, and concentrated to remove most of the THF. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford 18.3 g of the chiral auxiliary reagent. A portion of this reagent (8.0 g, 19.3 mmol) was dissolved in 300 mL of anhydrous THF and cooled to -78 °C. Next, LDA solution (1.2 eq) was added at -78 °C as a solution in 200 mL of THF. *t*-Butyl bromoacetate (3.4 mL, 1.2 eq) was added at -78 °C, and the reaction mixture was warmed slowly to -45 °C and stirred at that temperature for 3 h. It was then cooled to -78 °C and quenched with 2 eq of HOAc (2.2 mL). The reaction mixture was warmed to rt, diluted with H_2O and then concentrated to remove most of the THF. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (3:1 hexanes/EtOAc) afforded 8.70 g of the succinyl derivative. This material (8.7 g, 16.4 mmol) was dissolved in 100 mL of anhydrous THF and cooled to 0 °C. In a separate flask, benzyl alcohol (2.2 mL, 1.3 eq) was dissolved in 100 mL of anhydrous THF and cooled to 0 °C. *n*-BuLi (1.1 eq) was then added at 0 °C to this benzyl alcohol solution, and the resulting solution was stirred at 0 °C for 30 min. This freshly prepared alkoxide solution was then added at 0 °C to the succinyl derivative above. After 1h, the reaction was quenched with brine and concentrated to remove most of the THF. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (6:1 hexanes/EtOAc) afforded 6.10 g of the dibenzyl derivative.

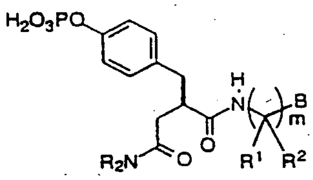
A portion of this dibenzyl derivative (1.80 g) was dissolved in 50 mL of EtOAc. 10% Pd-C (50 mg) was added and the resulting reaction mixture was stirred under 1 atm of H_2 for 24 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to afford 1.2 g of the desired acid (**61**). This acid could be subjected to the standard amide coupling, phosphorylation, and deprotection conditions (as in Coupling Conditions C and D) to afford the desired phosphate derivative.

62A. Compounds ZZB-ZZE



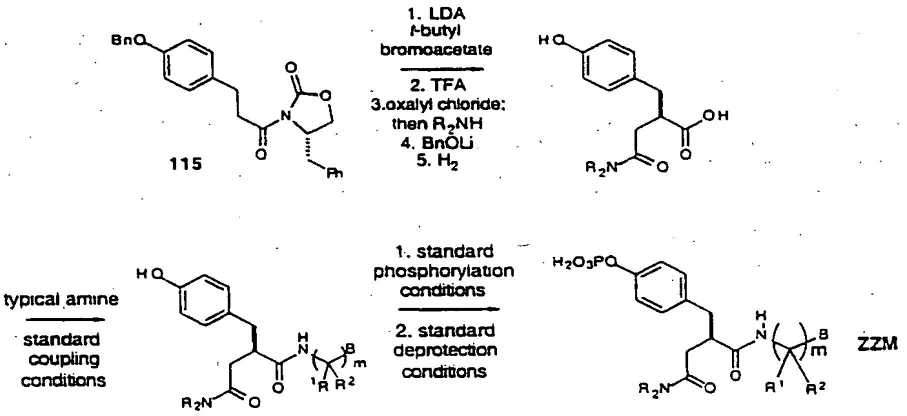
Compound	R^1	R^9	MS
ZZB	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	556 (M-H)
ZZC	$-CH_2OH$	$-CH_2(C_6H_4)$-4-CF_3	574 (M+H)
ZZD	$-CH_2OH$	$-CH_2(C_6H_4)$-3,4-Cl_2	574 (M+H)
ZZE	$-CH_3$	$-CH_2(C_6H_4)$-3,4-Cl_2	556 (M-H)

General Method WEA: Preparation of succimamide derivatives

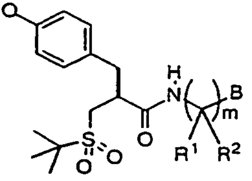


ZZM

Compounds such as Compounds ZZM (R = H or Me, for example) can be prepared according to the scheme below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G. for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies and is similar to General Method WE.

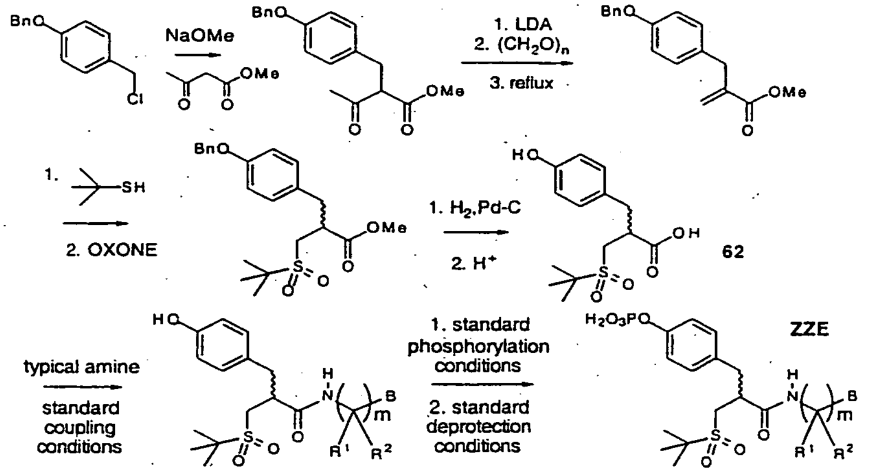

BnO
115
1. LDA
t-butyl bromoacetate
2. TFA
3.oxalyl chloride; then R2NH
4. BnOLi
5. H2
HO
OH
R2N
typical amine
standard coupling conditions
1. standard phosphorylation conditions
2. standard deprotection conditions
H2O3PO
B
m
R1
R2
ZZM

General Method WF: Preparation of sulfone tyrosine derivatives

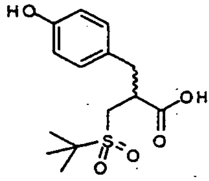


ZZE

Compounds such as Compounds ZZE can be prepared according to the scheme below using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies and is similar to General Method WE.



Preparation of Acid **62**

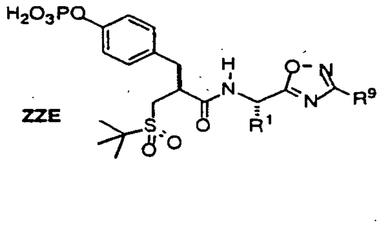


62

In a typical procedure, methyl acetoacetate (2.3 mL, 21.5 mmol) was dissolved in 20 mL of MeOH and 1 eq of NaOMe (0.5 M in MeOH, Aldrich) was added. The reaction mixture was stirred at rt for 15 min and 4-benzyloxy benzyl chloride was added. The resulting reaction mixture was stirred at reflux for 4 h. It was cooled to rt, quenched with H_2O and concentrated to remove most of the volatiles. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

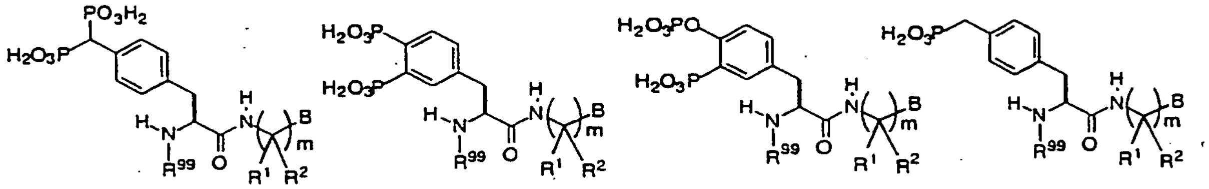
Purification by chromatography (6:1 hexanes/EtOAc) afforded 2.80 g of the alkylated product. This material was then dissolved in 30 mL of anhydrous THF and added at -78 °C to a freshly prepared solution of LDA in 30 mL of anhydrous THF. The reaction mixture was warmed to rt, and 1 g of paraformaldehyde was added. After stirring at rt for 1h, the reaction mixture was heated to a reflux for 4 h. It was then cooled to rt and filtered. The filtrate was concentrated, and the residue was stirred in 20 mL of saturated aqueous $NaHCO_3$ for 1h. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (neutral alumina, 3:1 hexanes/EtOAc) afforded 1.4 g of the alpha-beta unsaturated ester. This material was immediately dissolved in 50 mL of absolute ethanol and tert-butyl thiol (0.54 mL, 1 eq) was added. After 6 mg of NaH (60% by wt in mineral oil) was added, the reaction mixture was stirred at rt for 15 h. The reaction mixture was diluted with 40 mL of H_2O and OXONE (8.8 g, 3 eq, Aldrich) was added at 0 °C. The reaction mixture was warmed to rt and stirred for 15 h. It was then diluted with EtOAc and H_2O and stirred vigorously for 15 min. The mixture was filtered and the filtrate was concentrated. The resulting aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by chromatography (SiO_2, 1:1 hexanes/EtOAc) afforded 900 mg of the sulfone derivative. This sulfone was dissolved in 20 mL of EtOAc and 20 mL of MeOH, and 50 mg of 10% Pd/C was added. The reaction mixture was hydrogenated under 1 atm of H_2 at rt for 4 h. It was then filtered through Celite. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in 6 mL of 6N HCl and 2 mL of glacial acetic acid. The reaction mixture was heated at reflux for 15 h. It was then cooled to rt, diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 500 mg of the acid (**62**). This acid could be subjected to the standard amide coupling, phosphorylation, and deprotection to afford the desired phosphate derivative. The individual diastereomers could be separated by reverse-phase HPLC using a mixture of H_2O/CH_3CN containing 0.1% TFA.

62B. Compounds ZZG-ZZI


ZZE

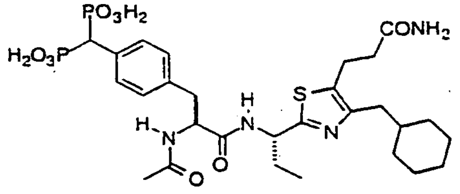
Compound	R^1	R^9	MS
ZZG	$-CH_3$	$-(CH_2)_5CH_3$	560 (M+H)
ZZH	$-CH_3$	$-CH_2(C_6H_4)$-4-CF_3	634 (M+H)
ZZI	$-(CH_2)_2CONH_2$	$-CH_2(C_6H_4)$-4-CF_3	689 (M-H)

General Method X: Preparation of phosphonate derivatives



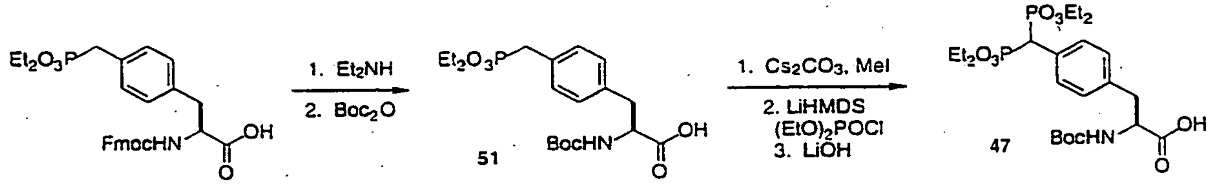
Compounds such as Compounds ZAA-ZAI can be prepared according to the preparation of Compound ZAA described below using the appropriate acid coupling partner along with the appropriate amine coupling partner. which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies. Use of the appropriate acylation reagent analogous to Method N provides R^{99}.

63. Compound ZAA



ZAA

Preparation of acid **47**



(a) p($CH_2PO_3Et_2$)-L-Phe-OH

Fmoc-p($CH_2PO_3Et_2$)-L-Phe-OH (5.0 g, 9.3 mmol) was dissolved in 170 mL of THF and 50 mL of diethyl amine, and the mixture was stirred vigorously at rt for 3 h. Solvents were removed under reduced pressure, and the solid was resuspended in anhydrous ether, filtered, and dried on high vacuum to afford 2.8 g (94%) of p($CH_2PO_3Et_2$)-L-Phe-OH as white solid, which was used without purification in the next step.

(b) N-Boc-p($CH_2PO_3Et_2$)-L-Phe-OH (**51**)

To a solution of p($CH_2PO_3Et_2$)-L-Phe-OH (5.0 g, 16.7 mmol) in a 1:1 mixture of DME/water (140 mL) at 0 °C was added $NaHCO_3$ (3.1 g, 36.8 mmol) followed by Boc_2O (4.0 g, 18.4 mmol). The mixture was stirred at 0 °C for 30 min, then warmed to rt and stirred for 1 h. About 50 mL of DME was removed by evaporation, and then the remaining aqueous solution was washed with EtOAc (2 x 50 mL). The aqueous layer was brought to pH 4 with 1 N HCl and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to a colorless oil (**51**) (6.2 g, 90%). MS [M - H] 414.

(c) N-Boc-p($CH_2PO_3Et_2$)-L-Phe-OMe

To a solution of N-Boc-p($CH_2PO_3Et_2$)-L-Phe-OH (5.1 g, 12.2 mmol) in DMF (60 mL) was added Cs_2CO_3 (4.8 g, 14.7 mmol) followed by MeI (0.76 mL, 12.2 mmol). The mixture was stirred for 1 h, diluted with water (600 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water, 10% $NaHSO_3$, dried over $MgSO_4$ and concentrated to a solid which was recrystallized from EtOAc/hexane to give a white solid (4.6 g, 88%). MS [M - H] 428. mp 104-105 °C.

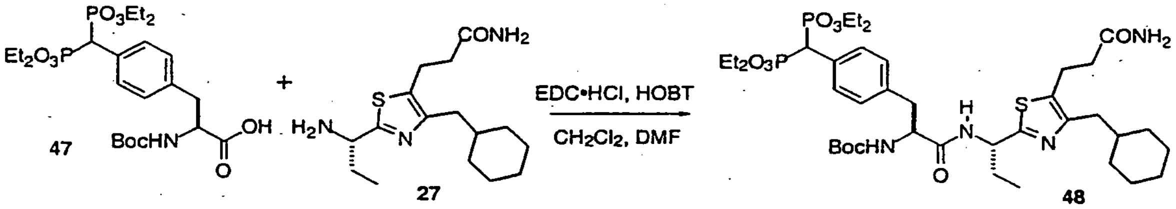
(d) N-Boc-p[$CH(PO_3Et_2)_2$]-L-Phe-OMe

To a suspension of N-Boc-p($CH_2PO_3Et_2$)-L-Phe-OMe (7.0 g, 16.3 mmol) in 185 mL of anhydrous DME, purged with N_2 and cooled to -42 °C (CH_3CN/dry ice), was added dropwise lithium bis(trimethylsilyl)amide (1 M THF, 48.9 mL, 48.9 mmol). The reaction mixture was stirred at -42 °C for 15 min. Diethyl chlorophosphate (4.7 mL, 32.6 mmol) was added, and the orange solution was stirred at -42 °C for an additional 20 min before being quenched with 1 N HCl (20 mL). The mixture was further diluted with water and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water, dried over $MgSO_4$, concentrated, and chromatographed over silica gel (3% $MeOH/CH_2Cl_2$) to give a colorless oil (6.0 g, 65%). MS [M - H] 564.

(e) N-Boc-p[CH(PO_3Et_2)$_2$]-L-Phe-OH

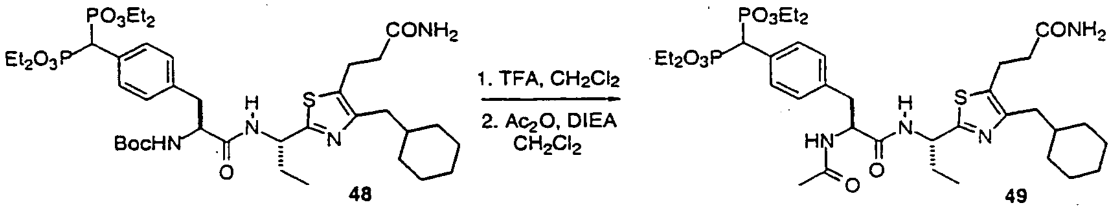
To a solution of N-Boc-p[CH(PO_3Et_2)$_2$]-L-Phe-OMe (0.490 g, 0.966 mmol) in 5 mL of THF cooled to 0 °C was added dropwise a solution of lithium hydroxide monohydrate (49.0 mg, 1.17 mmol) in 1.0 mL of water. The reaction mixture was stirred at 0 °C for 1 h. THF was removed under reduced pressure to give a yellow oil which was diluted with 10 mL of 1 N HCl. The aqueous phase was extracted with CH_2Cl_2 (8 x 15 mL), and the extracts were combined, dried over Na_2SO_4, and concentrated to afford 0.453 g (95%) of N-Boc-p[CH(PO_3Et_2)$_2$]-L-Phe-OH (**47**) as a crystalline white solid. MS [M - H] 550. mp 84-87 °C

Preparation of Compound **48**



(f) To 249 mg (0.451 mmol) of acid **47** in 10 mL of CH_2Cl_2 and 2.5 mL of DMF at RT was added a combined portion of 95 mg (0.497 mmol) of EDC•HCl and 76 mg (0.497 mmol) of HOBT. The resulting mixture was stirred at RT for 10 min, at which point 154 mg (0.497 mmol) of amine **27** (General Method E) was added in 1 portion.The resulting mixture was cooled to 0 °C. After stirring at 0 °C for 2 h, an additional 0.3 eq each of EDC•HCl and HOBT were added, and the reaction mixture was stirred for 1.1 h at RT (additional reagent had no effect by TLC analysis). At this point, the reaction mixture was partially concentrated and then diluted with EtOAc and 5% $NaHCO_3$. The organic layer was then washed with 10% citric acid and brine. The organic layer was then dried over Na_2SO_4 and concentrated. Flash chromatography (elution with 9:1 CH_2Cl_2-MeOH) gave 342 mg (90.1%) of a pale foam: R_f 0.52 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 MeCN/water) m/z 843 (M+H).

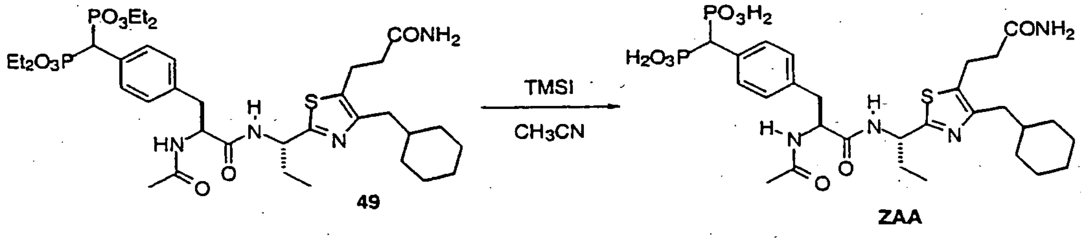
Preparation of Compound **49**



(g) To a solution of 342 mg (0.406 mmol) of Compound **48** in 2.5 mL of CH_2Cl_2 at RT was added 0.5 mL of TFA. The resulting mixture was stirred at RT for 2.3 h (additional TFA added at 1.25 h (0.2 mL) and 2 h (0.05 mL) as TLC analysis revealed the presence of starting material) and then concentrated. The resulting residue was taken five times through a sequence of dissolving in a small amount of CH_2Cl_2, concentration via a N_2 stream and concentration in vacuo. The resulting final residue was pumped on overnight. R_f 0.10 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 MeCN/water) m/z 743 (M+H).

(h) To the crude amine/TFA salt above in 4 mL of CH_2Cl_2 at 0 °C was added 0.057 mL (0.609 mmol) of Ac_2O followed by 0.212 mL (1.22 mmol) of DIEA. The resulting mixture was stirred at 0 °C for 2.5 h, then diluted with CH_2Cl_2 and washed with 10% $NaHCO_3$ followed by 1N HCl. Each of the washings was back extracted once with CH_2Cl_2. The combined organic layers were then washed once with brine and dried over Na_2SO_4, filtered through glass wool and concentrated. An additional amount of product was isolated separately from saturating the combined aqueous layers with $(NH_4)_2SO_4$ and extracting with CH_2Cl_2. Flash chromatography (separately again, elution with 9:1 CH_2Cl_2-MeOH) gave 249 mg (78.3% combined) of a pale foam: R_f 0.24 (9:1 CH_2Cl_2-MeOH). Electrospray Mass Spectrum (50/50 MeCN/water) m/z 785 (M+H).

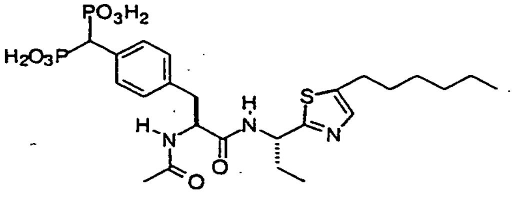
Preparation of Compound **ZAA**



(i) To 249 mg (0.317 mmol) of Compound **49** in 2.5 mL of CH_3CN at -20 °C was added 0.9 mL (6.34 mmol) of TMSI. The resulting mixture was stirred at -20 °C for 1.1 h whereupon an additional 0.2 mL of TMSI was added. The mixture was stirred an additional

15 min and quenched by the addition of 3 mL of 5% $NaHCO_3$ followed by 3 mL of DMF and several crystals of solid $Na_2S_2O_5$ to turn the dark orange color to pale yellow. Reverse phase HPLC followed by lyophilization gave 110 mg (51.6%) of a fluffy white solid. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 673 (M+H).

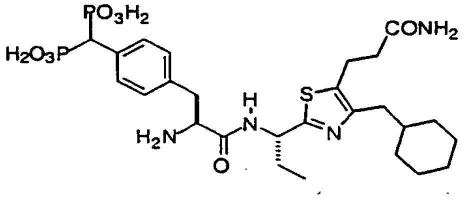
64. Compound ZAB



ZAB

Compounds such as Compound **ZAB** can be prepared according to General Method X, exemplified by the procedure described for the preparation of compound **ZAA** with the appropriate amine coupling partner, which can be prepared according to General Method E. Reverse phase HPLC followed by lyophilization gave a fluffy white solid. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 590 (M+H).

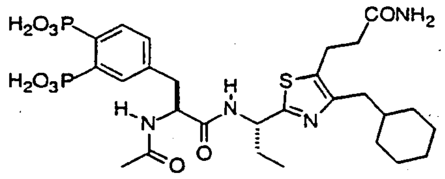
65. Compound ZAC



ZAC

Compounds such as Compound **ZAC** can be prepared directly from compounds such as Compound **48** according to the procedure for the preparation of Compound **ZAA** in General Method X. Reverse phase HPLC followed by lyophilization gave a fluffy white solid. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 631 (M+H).

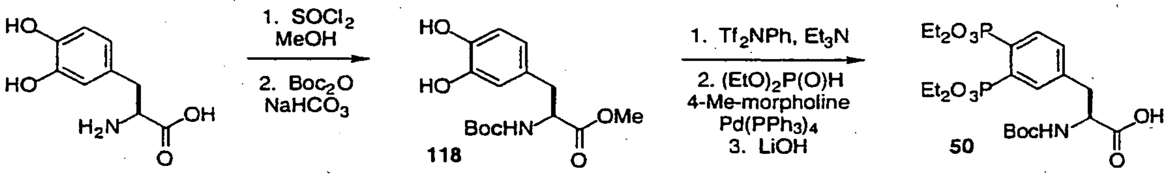
66. Compound ZAD



ZAD

Compounds such as Compound **ZAD** can be prepared according to General Method X, exemplified by the procedure described for the preparation of Compound **ZAA**, substituting the appropriate carboxylic acid coupling partner (**50** - see below) with the appropriate amine coupling partner (**27**), which can be prepared according to General Method E. Reverse phase HPLC followed by lyophilization gave a fluffy white solid. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 659 (M+H).

Preparation of acid coupling partner **50**.



(a) [3-(3,4-(Dihydroxyphenyl)-L-alanine] methyl ester

To 3-(3,4-(Dihydroxyphenyl)-L-alanine (5 g, 25.4 mmol MeOH (40 mL) at 0 °C was added thionyl chloride (3.8 mL, 50.7 mmol). The mixture was allowed to stir for 16 h at rt, and then the solvent was removed under reduced pressure. The resulting mixture was then diluted with water, and extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized from ethyl acetate/hexane (5 g, 92%). MS [M + H] 212.

(b) [3-(3,4-(Dihydroxyphenyl)-N-Boc-L-alanine] methyl ester (**118**)

To [3-(3,4-(Dihydroxyphenyl)-L-alanine] methyl ester (5.4 g, 25.4 mmol) and di-tert-butyl dicarbonate (5.5 g, 25.4 mmol) in a mixture of THF (20 mL) and water (20 mL) at rt was added sodium bicarbonate (3.2 g, 38.1 mmol). The mixture was allowed to stir for 16 h and then washed with water and extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized from ethyl acetate/hexane (7 g, 88%). MS [M + H] 312.

(c) [3-(3,4-(Ditrifluoromethanesulfonyloxyphenyl)-N-Boc-L-alanine] methyl ester

To [3-(3,4-(Dihydroxyphenyl)-N-Boc-L-phenylalanine] methyl ester (**118**) (12 g, 38.6 mmol) and triethylamine (13 mL, 88.7 mmol) in methylene chloride (100 mL) at 0 °C was added N-phenyl-bis(trifluoromethanesulfonimide) (31.6 g, 88.7 mmol). The mixture was allowed to stir for two days and then washed sequentially with 1 N NaOH, 1 N HCl, and brine. The organic layer was dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized frome dichloromethane/hexane. MS [M + Na] 598.

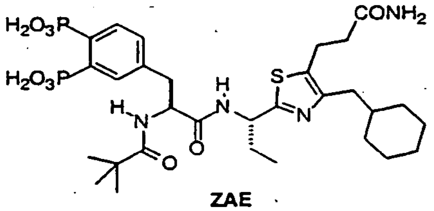
(d) 3,4-(Diethylphosphonyl)-N-Boc-L-phenylalanine methyl ester

To [3-(3,4-(Ditrifluoromethanesulfonyloxyphenyl)-N-Boc-L-alanine] methyl ester (2 g, 3.47 mmol), diethyl phosphite (1 mL, 7.65 mmol) and 4-methyl morpholine (0.93 mL, 8.3 mmol) in MeCN (10 mL) was added $Pd(Ph_3)_4$ (167 mg, 0.15 mmol). The mixture was allowed to stir for two days at 95 °C. It was then diluted with saturated NH_4Cl and extracted with EtOAc. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed over silica gel (5% MeOH/EtOAc) to an oil (0.2 g, 37% yield). MS [M + H] 552 and [M + Na] 574.

(e) 3,4-(Diethylphosphonyl)-N-Boc-L-phenylalanine

Acid **50** can be prepared from 3,4-(Diethylphosphonyl)-N-Boc-L-phenylalanine methyl ester with LiOH according to the method described above for the preparation of acid **47** as in General Method X-(e).

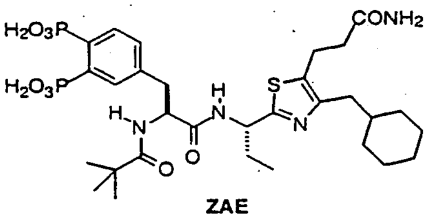
67. Compound ZAE



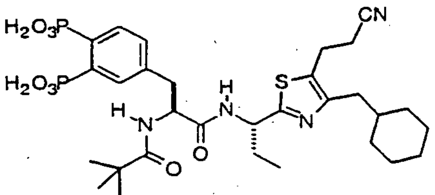
ZAE

Compounds such as compound **ZAE** can be prepared according to General Method X, exemplified by the procedure described for the preparation of compounds **ZAA** and **ZAD**, substituting pivaloyl anhydride for acetic anhydride in the step analogous to that for the preparation of Compound **49** as in General Method X-(h).

68. Compounds ZAF and ZAE

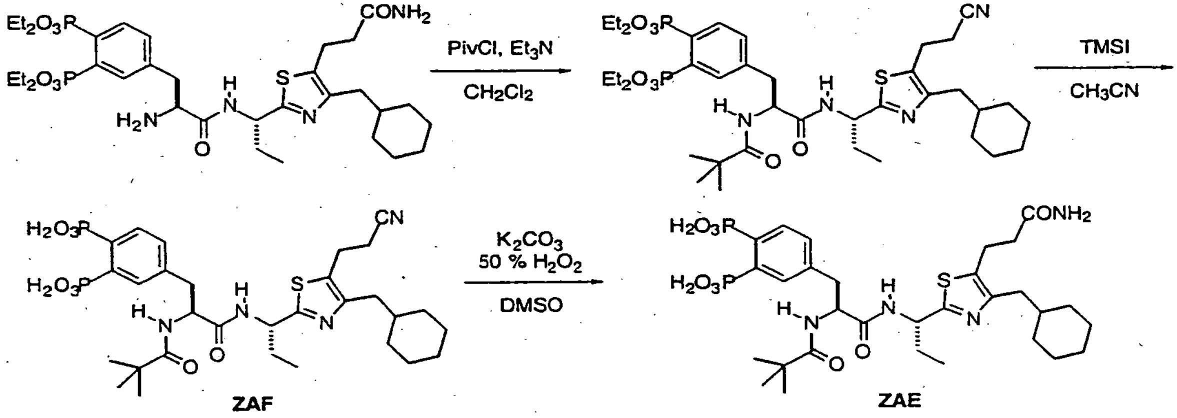


ZAE

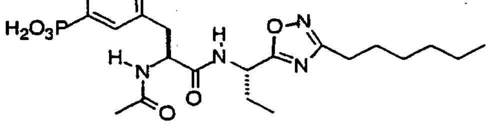


ZAF

Alternatively, compounds such as Compound **ZAE** and Compound **ZAF** can be prepared according to General Method X, exemplified by the procedure described for the preparation of Compounds **ZAA** and **ZAE** with the appropriate modifications according to the scheme shown below. Reverse phase HPLC of either Compound **ZAE** or Compound **ZAF** followed by lyophilization gave a fluffy white solid. Compound **ZAE**: Electrospray Mass Spectrum (50/50 MeCN/water) m/z 701 (M+H). Compound **ZAF**: Electrospray Mass Spectrum (50/50 MeCN/water) m/z 683 (M+H).



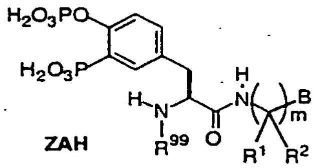
69. Compound ZAG



ZAG

Compounds such as Compound **ZAG** can be prepared according to General Method X, exemplified by the procedure described for the preparation of Compound **ZAA**, substituting the appropriate carboxylic acid coupling partner (50) with the appropriate amine coupling partner, which can be prepared according to General Method G. Reverse phase HPLC followed by lyophilization gave a fluffy white solid. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 559 (M-H).

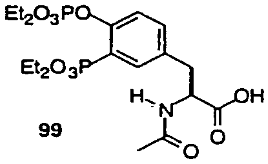
70. Compound ZAH



ZAH

Compounds such as Compound **ZAH** can be prepared according to General Method X, exemplified by the procedure described for the preparation of Compound **ZAA**, substituting the appropriate carboxylic acid coupling partner (**99**) with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example.

Preparation of acid coupling partner **99**



99

(a) 2-Acetylamino-3-(3-bromo-4-hydroxy-phenyl)-propionic acid methyl ester

To N-acetyl-L-tyrosine methyl ester (6 g, 25.3 mmol) in THF (60 mL) at rt was added N-bromosuccinimide (5.4 g, 30.3 mmol) followed by five drops of sulfuric acid. The mixture was stirred for 16 h at rt. The solvent was removed under reduced pressure and then water was added. The aqueous layer was extracted twice with EtOAc, and the combined extracts were dried over magnesium sulfate and concentrated to a solid. The solid was recrystallized from ethyl acetate/hexane (6 g, 75%). MS [M + H] 316.

(b) 2-Acetylamino-3-[3-(diethoxy-phosphoryl)-4-hydroxy-phenyl]-propionic acid methyl ester

To 2-acetylamino-3-(3-bromo-4-hydroxy-phenyl)-propionic acid methyl ester (3 g, 9 mmol), diethyl phosphite (1.6 mL, 11 mmol) and 4-methylmorpholine (1.5 mL, 13.5 mmol) in toluene (10 mL) and MeCN (10 mL) was added $Pd(Ph_3)_4$ (0.5 g, 0.45 mmol). The mixture was allowed to stir for two days at 100 °C. It was then diluted with saturated NH_4Cl and extracted with EtOAc. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed over silica gel (5% $MeOH/CHCl_3$) affording an oil. MS [M + H] 374 and [M - H] 372.

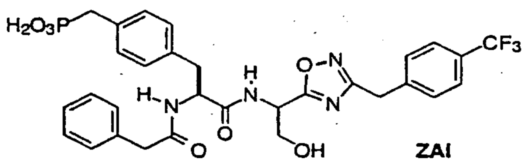
(c) 2-Acetylamino-3-[3-(diethoxy-phosphoryl)-4-(diethoxy-phosphoryloxy)-phenyl]-propionic acid methyl ester

To 2-Acetylamino-3-[3-(diethoxy-phosphoryl)-4-hydroxy-phenyl]-propionic acid methyl ester (0.15 g, 0.25 mmol) in MeCN (10 mL) was added diethyl chlorophosphate (0.05 mL, 0.3 mmol) followed by K_2CO_3 (0.07 g, 0.5 mmol) at rt. The reaction was stirred for 4 h before H_2O (10 mL) and EtOAc (20 mL) were added. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed over silica gel (20% $MeOH/CHCl_3$) affording an oil. MS [M + H] 510.

(d) 2-Acetylamino-3-[3-(diethoxy-phosphoryl)-4-(diethoxy-phosphoryloxy)-phenyl]-propionic acid (**99**)

Acid **99** can be prepared from 2-acetylamino-3-[3-(diethoxy-phosphoryl)-4-(diethoxy-phosphoryloxy)-phenyl]-propionic acid methyl ester with LiOH according to the method described above for the preparation of acid **47**.

71. Compound ZAI

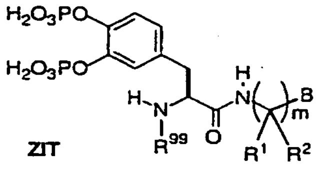


ZAI

Compounds such as Compound **ZAI** can be prepared according to General Method X, exemplified by the procedure described for the preparation of Compound **ZAA**, substituting the appropriate carboxylic acid coupling partner, **51** from General Method X-

(b), with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. Electrospray Mass Spectrum (50/50 MeCN/water) m/z 647 (M+H).

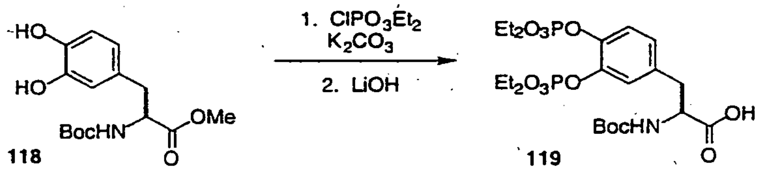
General Method XA: Preparation of bisphosphate derivatives



ZIT

Compounds such Compound ZIT can be prepared according to General Method X using the appropriate acid coupling partner (**119**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C with obvious differences in protecting group strategies. Use of the appropriate acylation reagent analogous to Method N provides R^{99}.

Preparation of Acid **119**



118 119

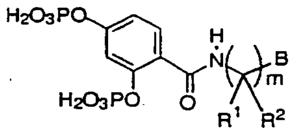
(a) 3-(S)-[3,4-Bis-(diethoxy-phosphoryloxy)-phenyl]-2-tert-butoxycarbonylamino-propionic acid methyl ester

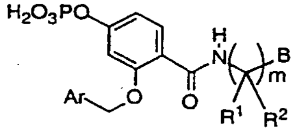
To 2-tert-Butoxycarbonylamino-(S)-3-(3,4-dihydroxy-phenyl)-propionic acid methyl ester (**118**) (2 g, 6.4 mmol) in MeCN (30 mL) was added diethyl chlorophosphate (1.1 mL, 7.7 mmol) followed by K_2CO_3 (3.5 g, 25.6 mmol) at rt. The reaction was stirred for 8 h before H_2O (50 mL) and EtOAc (50 mL) were added. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed over silica gel (5% MeOH/$CHCl_3$) affording an oil (2.3 g, 62%). MS [M + H] 584.

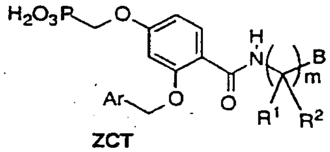
(c) 3-(S)-[3,4-Bis-(diethoxy-phosphoryloxy)-phenyl]-2-tert-butoxycarbonylamino-propionic acid (**119**)

The title compound (**119**) can be prepared from 3-(S)-[3,4-Bis-(diethoxy-phosphoryloxy)-phenyl]-2-tert-butoxycarbonylamino-propionic acid methyl ester with LiOH according to the method described previously for the preparation of acid **47** in General Method X-(h). The product was obtained as a colorless powder. Electrospray Mass Spectrum (50/50 acetonitrile/water + 0.1% ammonium hydroxide) MS [M + H] 673.

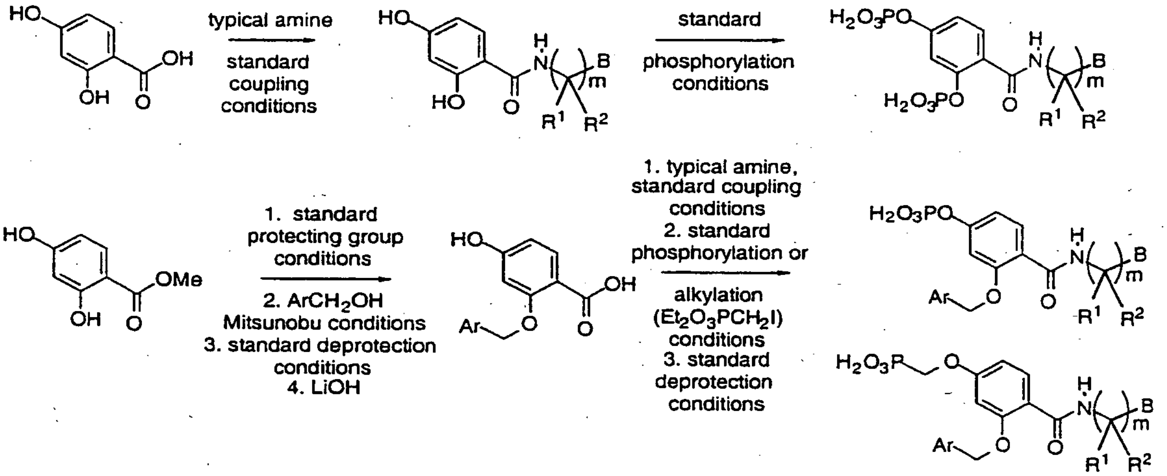
General Method XB: Preparation of other phosphate derivatives


ZAT

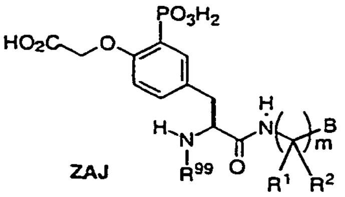

ZBT


ZCT

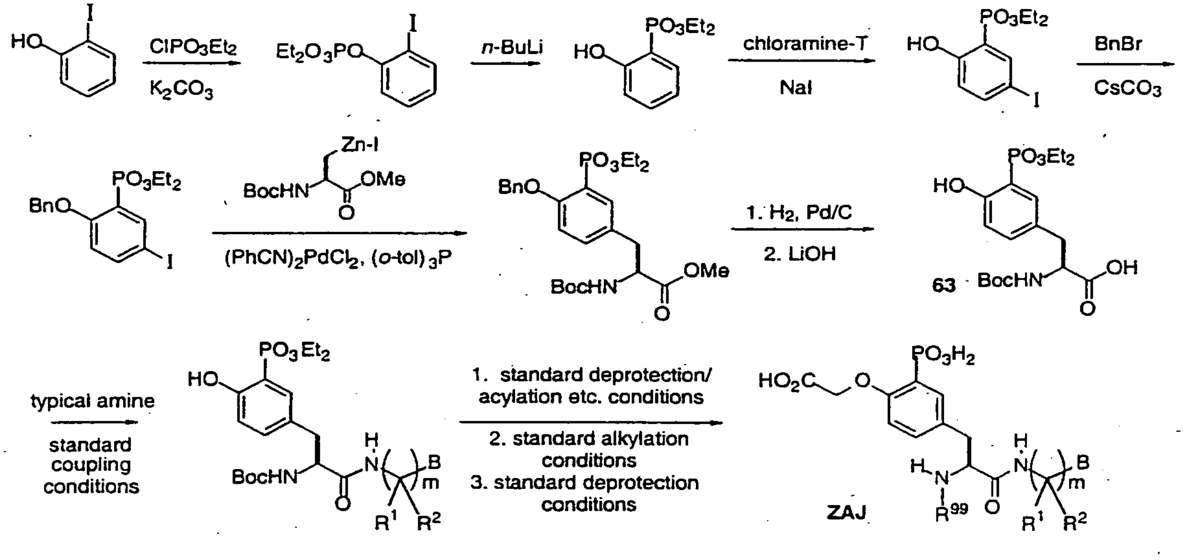
Compounds such as Compounds ZAT-ZCT can be prepared according to the following scheme using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.


typical amine
standard coupling conditions
standard
phosphorylation conditions
1. standard protecting group conditions
2. ArCH2OH Mitsunobu conditions
3. standard deprotection conditions
4. LiOH
1. typical amine, standard coupling conditions
2. standard phosphorylation or
alkylation (Et2O3PCH2I) conditions
3. standard deprotection conditions

General Method Y: Preparation of acetic acid phosphonate derivatives

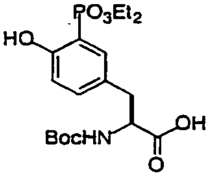

ZAJ

Compounds such as Compounds **ZAJ** can be prepared according to the scheme below using the appropriate acid coupling partner (**63**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies and is similar to General Method WD.

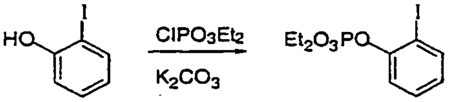


HO
I
$ClPO_3Et_2$
K_2CO_3
Et_2O_3PO
n-BuLi
PO_3Et_2
chloramine-T
NaI
BnBr
$CsCO_3$
BnO
Zn-I
BocHN
OMe
O
$(PhCN)_2PdCl_2$, (o-tol)$_3$P
1. H_2, Pd/C
2. LiOH
63
OH
typical amine
standard coupling conditions
H
N
B
m
R^1
R^2
1. standard deprotection/ acylation etc. conditions
2. standard alkylation conditions
3. standard deprotection conditions
HO_2C
PO_3H_2
ZAJ
R^{99}

Preparation of acid coupling partner **63**

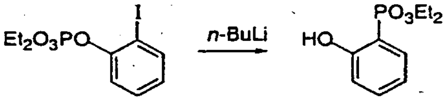

63

(a) Phosphoric acid diethyl ester 2-iodo-phenyl ester



To a mixture of 2-iodophenol (14.1 g, 64.1 mmol) and potassium carbonate (17.6 g, 128 mmol) in MeCN (100 mL) was added diethyl chlorophosphate (11.1 mL, 76.7 mmol). The mixture was allowed to stir at RT for 5 h. The solvent was removed under reduced pressure, and the residue diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (elution with a stepwise gradient 25-40% EtOAc-hexanes) to give 21.7 g (95%) of a pale oil. R_f 0.47 (1:1 EtOAc-hexanes). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 357 (M+H).

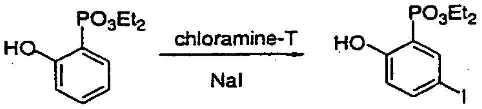
(b) (2-hydroxy-phenyl)-phosphonic acid diethyl ester



(2-Hydroxy-phenyl)-phosphonic acid diethyl ester was prepared according to Casteel, D. A.; Peri, S. P. *Synthesis* **1991**, 691.

To a cooled (-78 °C) solution of phosphoric acid diethyl ester 2-iodo-phenyl ester (21.7 g, 61.0 mmol) in dry THF (500 mL) under N_2 was added a 2.5 M solution of *n*-BuLi (40 mL, 100 mmol). After 20 min, the reaction was treated with satd aq NH_4Cl (50 mL) and allowed to warm to RT. The mixture was diluted with H_2O (50 mL) and extracted twice with EtOAc. The organic extracts were pooled, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (20% EtOAc-hexanes) to give 13.1 g (93%) of a pale oil. R_f 0.60 (1:1 EtOAc-hexanes). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 231 (M+H).

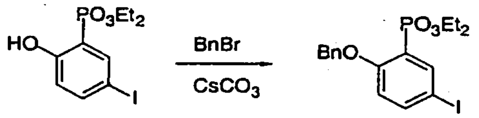
(c) (2-hydroxy-5-iodo-phenyl)-phosphonic acid diethyl ester



(2-Hydroxy-5-iodo-phenyl)-phosphonic acid diethyl ester was prepared according to Kometani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 691.

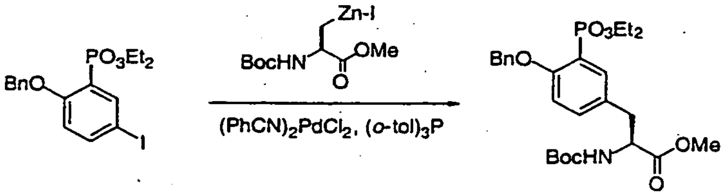
To a cooled (0 °C) mixture of (2-hydroxy-phenyl)-phosphonic acid diethyl ester (13.1 g, 56.9 mmol) and NaI (10.2 g, 68.3 mmol) in DMF (200 mL) was added chloramine-T trihydrate (19.2 g, 68.3 mmol) over 5 min. The ice bath was removed after 10 min, and the mixture was allowed to stir at RT for 2 h. The mixture was diluted with H_2O (50 mL), acidified using 0.5 N HCl and extracted twice with EtOAc. The organic extracts were pooled and washed sequentially with satd. $Na_2S_2O_3$/brine (1/1) and then brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (elution with a stepwise gradient 5-15% EtOAc-hexanes) to give 14.9 g (73%) of a colorless solid after recrystallization (EtOAc-hexanes). R_f 0.30 (20% EtOAc-hexanes). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 357 (M+H).

(d) (2-benzyloxy-5-iodo-phenyl)-phosphonic acid diethyl ester



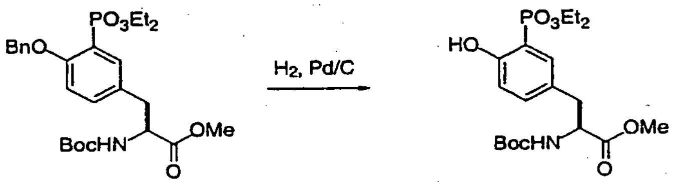
To a mixture of (2-hydroxy-5-iodo-phenyl)-phosphonic acid diethyl ester (14.7 g, 41.2 mmol) and Cs_2CO_3 (17.4 g, 53.5 mmol) in DMF (150 mL) was added benzyl bromide (6.40 mL, 54 mmol). The reaction was allowed to stir for 2.5 days at RT at which point the reaction was concentrated under reduced pressure. The residue was diluted with 0.5 N HCl (30 mL) and extracted twice with EtOAc. The pooled organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 17.4 g (91%) of a colorless solid after recrystallization (EtOAc-hexanes). R_f 0.36 (1:1 EtOAc-hexanes). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 447 (M+H).

(e) 3-[4-benzyloxy-3-(diethoxy-phosphoryl)-phenyl]-(*S*)-2-*tert*-butoxycarbonylamino-propionic acid methyl ester



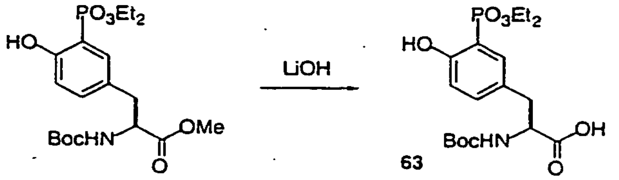
To a mixture of Zn dust (403 mg, 6.17 mmol) in dry DMA (1 mL) and dry THF (1 mL) was added dibromoethane (0.055 mL, 0.64 mmol) and chlorotrimethylsilane (0.080 mL, 0.63 mmol). The mixture was sonicated for 15 min under N_2. To this mixture was added a solution of Boc-iodoalanine-methyl ester (1.45 g, 4.41 mmol) in dry DMA (1 mL) and dry THF (1 mL). The mixture was sonicated for 30 min and then heated (65 °C) for 45 min under N_2. To the heated mixture was added a solution (2-benzyloxy-5-iodo-phenyl)-phosphonic acid diethyl ester (1.37 g, 2.94 mmol), *bis*(benzonitrile)dichloropalladium (II) (67 mg, 0.17 mmol) and tri-*ortho*-tolylphosphine (148 mg, 0.486 mmol) in dry DMA (1 mL) and THF (1 mL) over 5 min. The mixture was allowed to stir for 3 h at 65 °C under N_2 at which point it was allowed to cool to RT, diluted with 0.5 N HCl and extracted twice with Et_2O. The organic extracts were pooled, washed with brine, filtered through Celite, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. An initial chromatographic purification over silica gel (elution with a stepwise gradient 15-40% acetone-hexanes) was followed by a second chromatographic purification over silica gel (70% EtOAc-hexanes) to give 958 mg (63%) of a pale oil. R_f 0.33 (80% EtOAc-hexanes). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 520 (M-H).

(f) (*S*)-2-*tert*-butoxycarbonylamino-3-[3-(diethoxy-phosphoryl)-4-hydroxy-phenyl]-propionic acid methyl ester



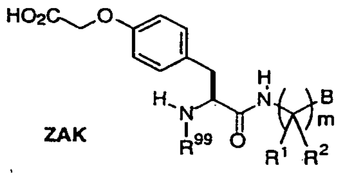
To a solution of 3-[4-benzyloxy-3-(diethoxy-phosphoryl)-phenyl]-(*S*)-2-*tert*-butoxycarbonylamino-propionic acid methyl ester (956 mg, 1.84 mmol) in MeOH (50 mL) was added 10% Pd/C (50 mg). The mixture was degassed under reduced pressure and allowed to stir at RT under H_2 for 18 h. The catalyst was removed by filtration through Celite, and the filtrate concentrated under reduced pressure. The residue was chromatographed over silica gel (elution with 35% EtOAc-hexanes) to give 782 mg (99%) of a colorless oil. R_f 0.41 (1:1 EtOAc-hexanes). Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 432 (M+H).

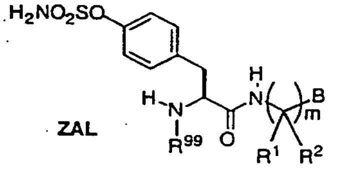
(g) (*S*)-2-*tert*-butoxycarbonylamino-3-[3-(diethoxy-phosphoryl)-4-hydroxy-phenyl]-propionic acid (**63**)



To a cooled (0 °C) solution (*S*)-2-*tert*-butoxycarbonylamino-3-[3-(diethoxy-phosphoryl)-4-hydroxy-phenyl]-propionic acid methyl ester (423 mg, 0.98 mmol) in MeOH (4 mL) was added LiOH monohydrate (84 mg, 2.0 mmol) in H_2O (4 mL). After 1 h, the ice bath was removed and the reaction was allowed to stir at RT for 1.5 h. The solution was carefully acidified to pH 2 using 0.5 N HCl and extracted twice with EtOAc. The organic extracts were pooled, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give 379 mg (91%) of a yellow foam. The crude material was carried on without further purification. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 416 (M-H).

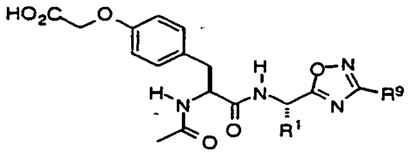
General Method Z: Preparation of O-sulfur and O-alkyl derivatives


ZAK


ZAL

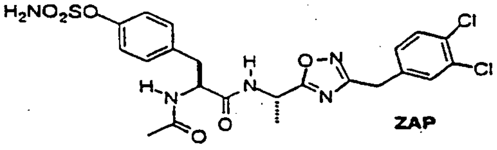
Compounds with substitution other than phosphate such as Compounds ZAK and ZAL can be prepared according to General Method Y, substituting the appropriate carboxylic acid coupling partner (N-acetyl tyrosine, for example) with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. O-derivatization can be performed via standard O-alkylation (as in General Method W) and O-sulfonamidation (as in General Method K), for example.

72. Compounds ZAM-ZAO



Compound	R^1	R^9	MS
ZAM	-CH_2-(3-indole)	-$(CH_2)_5CH_3$	574 (M-H)
ZAN	-$(CH_2)_2CO_2H$	-CH_2Chx	531 (M+H)
ZAO	-$(CH_2)_2CO_2H$	-$(CH_2)_5CH_3$	519 (M-H+H_2O)

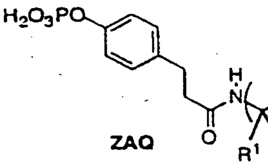
73. Compound ZAP



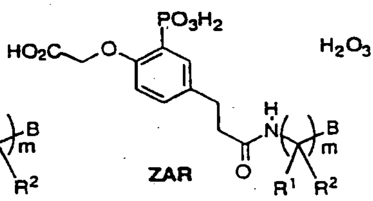
ZAP

Compounds such as Compound ZAP can be prepared according to General Method Z. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 555 (M-H).

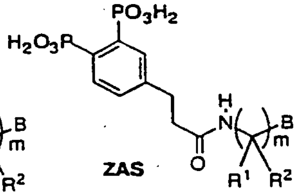
General Method ZA: Preparation of hydrocinnamic acid phosphate and phosphonate analogs



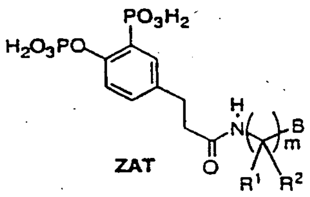
ZAQ



ZAR



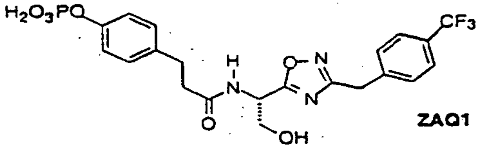
ZAS



ZAT

Compounds such as Compounds ZAQ-ZAT can be prepared according to General Methods such as General Methods C, D, X and Y, for example, with obvious substitution of the appropriate 3-(4-hydroxyphenyl)propionic acid derivative as starting material.

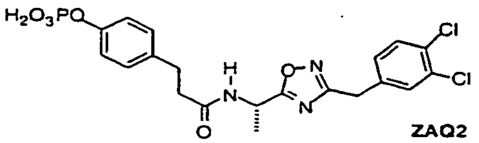
74. Compound ZAQ1



ZAQ1

Compounds such as Compound ZAQ1 can be prepared according to General Method ZA. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 514 (M-H).

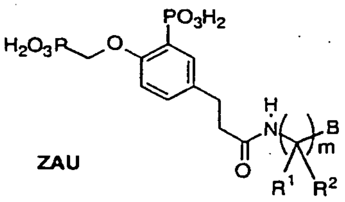
75. Compound ZAQ2



ZAQ2

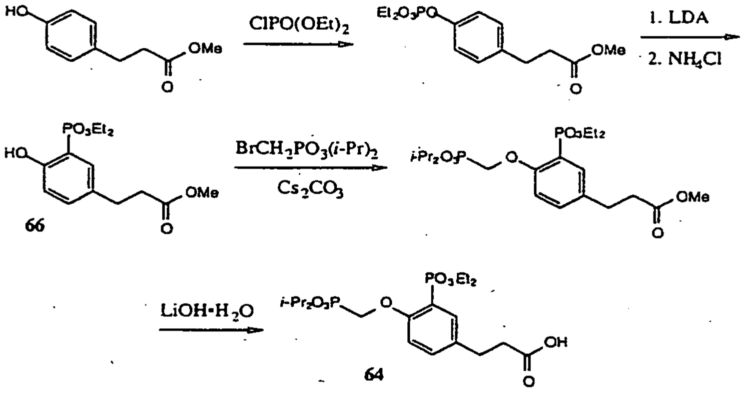
Compounds such as Compound ZAQ2 can be prepared according to General Method ZA. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 499 (M-H).

General Method ZB: Preparation of hydrocinnamic acid phosphonate analogs

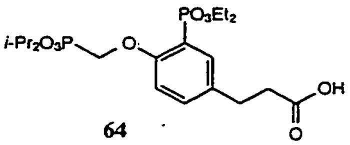


ZAU

Compounds such as Compound ZAU can be prepared according to General Method ZA, substituting the appropriate acid (**64**) which can be prepared according to the scheme shown below.



Preparation of acid coupling partner **64**



64

(a) 3-(4-Diethoxy-phosphoryl-oxyphenyl) propionic acid methyl ester

To methyl 3-(4-hydroxyphenyl) propionate (11 g, 61 mmol) in dry ether (250 mL) at 0 °C, was added NaH (1.8g, 75 mmol) portionwise. The reaction mixture was stirred at room temperature for 1 h and then diethyl chlorophosphate (10.6 mL, 73 mmol) was added. Stirring was continued for another 2 h. The reaction was quenched by slow addition of water. The layers were separated and the aqueous layer was extracted with ether twice. The combined organic layers were washed with 4 N NaOH, brine and dried over $MgSO_4$. Removal of the solvent resulted in the crude product as a colorless oil (19.0 g, 98%).

(b) 3-(3-Diethoxy-phosphoryl-4-hydroxyphenyl) propionic acid methyl ester (**66**)

To a solution of diisopropylamine (7.2 mL, 52.1 mmol) in dry THF (200 mL) at -78 °C was added *n*-BuLi (32.8 mL, 1.6 M in hexanes, 52.5 mmol) via syringe. The reaction was stirred at -78 °C for 30 min. 3-(4-Diethoxy-phosphoryloxyphenyl) propionic acid methyl ester (4.66 g, 14.7 mmol) in dry THF (250 mL) was added via cannula. Stirring was continued at -78 °C for 1 h. The reaction was allowed to warm to room temperature and then quenched with saturated NH_4Cl (50 mL). The mixture was extracted with ether 3 times, and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography over silica gel (50% EtOAc/hexane, $R_f = 0.43$) to give product (**66**) as a clear oil (2.3 g, 50%).

(c) 3-(3-Diethoxyphosphoryl-4-diisopropoxyphosphorylmethoxyphenyl) propionic acid methyl ester

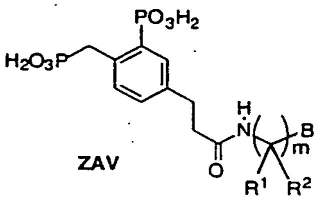
3-(3-Diethoxyphosphoryl-4-hydroxphenyl) propionic acid methyl ester (**66**) (316 mg, 1 mmol) was dissolved in 4 mL of DMF, and Cs_2CO_3 (429 mg, 1.32 mmol) was added, followed by diisopropyl bromomethylphosphonate (337 mg, 1.32 mmol). The reaction mixture was stirred at 75 °C under N_2 overnight. The reaction mixture was then partitioned between EtOAc and H_2O and the organic layer was dried over Na_2SO_4 and concentrated. The residue was further purified by flash column chromatography over silica gel (10% MeOH/EtOAc, $R_f = 0.45$) to obtain the pure product as a clear oil (474 mg, 96%).

(d) 3-(3-Diethoxyphosphoryl-4-diisopropoxyphosphoryl-methoxyphenyl) propionic acid (**64**)

To a solution of 3-(3-Diethoxyphosphoryl-4-diisopropoxyphosphoryl-methoxyphenyl) propionic acid methyl ester (474 mg, 0.96 mmol) in 5 mL THF at 0 °C was added

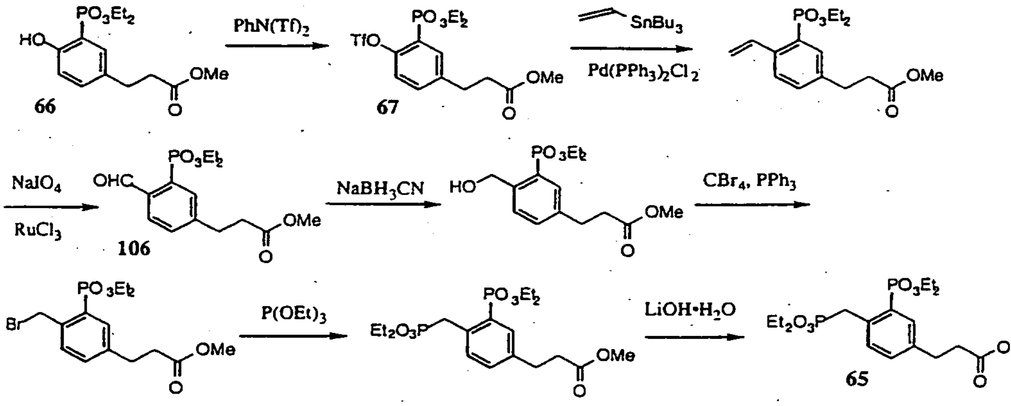
LiOH•H_2O (60 mg, 1.43 mmol) in 1 mL H_2O. The reaction mixture was stirred at 0 °C for 1 h. THF was removed *in vacuo* and 5 mL 1N HCl was added. The aqueous phase was extracted with DCM (8 X 10 mL). The combined organics were dried over Na_2SO_4 and concentrated to yield crude **64** (400 mg, 87%) as a clear oil. Electrospray mass spectrum: m/z 479.50 (M-H).

General Method ZC: Preparation of hydrocinnamic acid phosphonate analogs

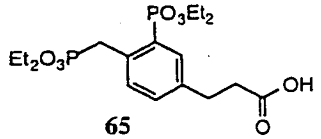


ZAV

Compounds such as Compound ZAV can be prepared according to General Method ZA, substituting the appropriate acid (**65**) which can be prepared according to the scheme shown below.



Preparation of acid coupling partner **65**



65

(a) 3-(3-diethoxyphosphoryl-4-trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester (**67**)

3-(3-Diethoxyphosphoryl-4-hydroxyphenyl)-propionic acid methyl ester (**66**) (3.16 g, 10 mmol) and $PhNTf_2$ (3.93 g, 11 mmol) were dissolved in 30 mL dry DCM. The mixture was cooled to 0 °C, and NEt_3 (1.67 mL, 12 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then slowly warmed to rt. The reaction mixture was diluted with 85 mL ether, and then washed with H_2O, 1 N NaOH, H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatograghy over silica gel (EtOAc/hexane 3:1, $R_f = 0.38$) to obtain an oil (3.41 g 78%).

(b) 3-(3-Diethoxyphosphoryl-4-vinyl-phenyl) propionic acid methyl ester

3-(3-diethoxyphosphoryl-4-trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester (**67**) (1 g, 2.23 mmol) was dissolved in dry dioxane (25 mL) together with vinyl tributyltin (0.67 mL, 2.29 mmol), LiCl (283 mg, 6.7 mmol), $Pd(PPh_3)_2Cl_2$ (47 mg, 0.067 mmol) and a crystal of 2,6-di-*tert*-butyl-4-methylphenol. The reaction mixture was degassed with argon, heated to 98 °C and allowed to stir for 2 h. The reaction mixture was then cooled to rt and diluted with excess ether and 10 mL saturated aqeous KF solution. The resulting mixture was stirred at rt overnight. The mixture was then filtered through Celite, and the layers were separated. The organic layer was washed with 1 N HCl and brine, dried over Na_2SO_4 and concentrated. The brownish oil was purified by flash column chromatography (EtOAc/hexane 90:10, $R_f = 0.50$) to give an oil (470 mg, 65%).

(c) 3-(3-Diethoxyphosphoryl-4-formyl-phenyl) propionic acid methyl ester

3-(3-Diethoxyphosphoryl-4-vinyl-phenyl) propionic acid methyl ester (200 mg, 0.61 mmol) was dissolved in 3.9 mL CCl_4 and 3.9 mL of MeCN. A solution of $NaIO_4$ (388 mg, 1.81 mmol) in 6 mL H_2O was added. The mixture was stirred vigorously and $RuCl_3$ (10 mg, 0.05 mmol) was then added. The mixture was stirred for 1 h at rt. The reaction mixture was diluted with DCM, and the organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography over silica gel (4/1 EtOAc/hexane, $R_f = 0.37$) to give pure product as an oil (153 mg, 76%).

(d) 3-(3-Diethoxyphosphoryl-4-hydroxymethyl-phenyl) propionic acid methyl ester

3-(3-Diethoxyphosphoryl-4-formyl-phenyl) propionic acid methyl ester (328.3 mg, 1 mmol) and $NaBH_3CN$ (67.0 mg, 1.1 mmol) were dissolved in 3 mL MeOH. A trace of methyl orange was added, and 2 N HCl/MeOH was then added dropwise with stirring to maintain the red color. After ca. 15 min. the color changed very slowly. The stirring was continued for an additional 45 min when the solvent was evaporated. The residue was taken up in 3 mL of H_2O, saturated with NaCl, and extracted with 3 mL (4 times) of ether. The combined organic layers were dried over $MgSO_4$ and concentrated to give crude product (330 mg, 100%).

(e) 3-(3-Diethoxyphosphoryl-4-bromomethyl-phenyl) propionic acid methyl ester

3-(3-Diethoxyphosphoryl-4-hydroxymethyl-phenyl) propionic acid methyl ester (330 mg, 1 mmol), PPh_3 (289 mg, 1.1 mmol) and CBr_4 (365 mg, 1.1 mmol) were dissolved in 5 mL dry THF. The reaction mixture was stirred at 25 °C for 1 h. The mixture turned cloudy. The mixture was filtered, and the filtrate concentrated. The residue was purified by flash column chromatography over silica gel (EtOAC/hexane 3/1, $R_f = 0.40$). Pure product was obtained as an oil (150 mg, 38%).

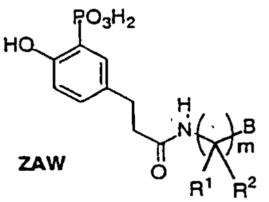
(f) 3-(3-Diethoxyphosphoryl-4-diethoxyphosphorylmethyl-phenyl) propionic acid methyl ester

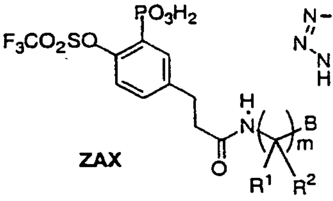
3-(3-Diethoxyphosphoryl-4-bromomethyl-phenyl) propionic acid methyl ester (150 mg, 0.38 mmol) was dissolved in $P(OEt)_3$ (2 mL, 11.4 mmol) and the reaction mixture was heated at 130 °C for 1 h. The volatile component was evaporated by N_2 flow. The product was obtained as a clear oil (172 mg, 100%).

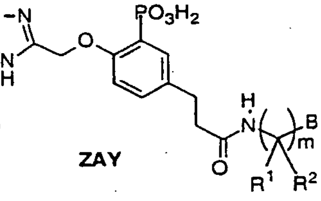
(g) 3-(3-Diethoxyphosphoryl-4-diethoxyphosphorylmethyl-phenyl) propionic acid **(65)**

This compound can be prepared according to the standard LiOH procedure described in General Method ZB (d).

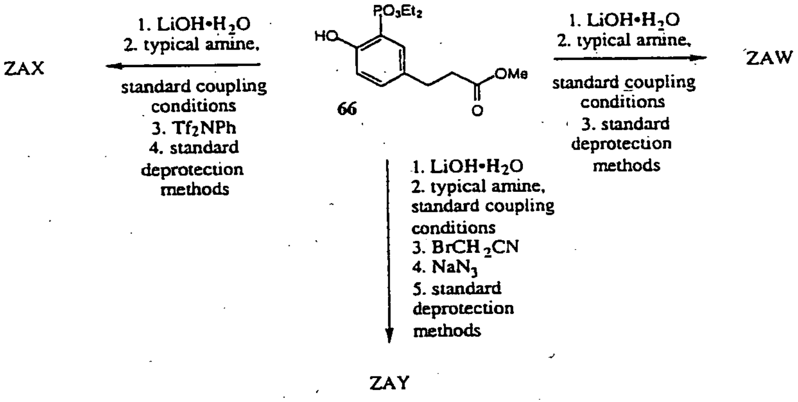
General Method ZD: Preparation of hydrocinnamic acid phosphonate analogs


ZAW

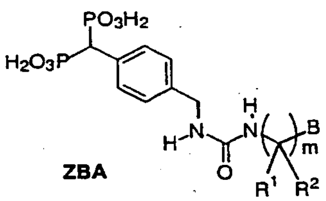

ZAX

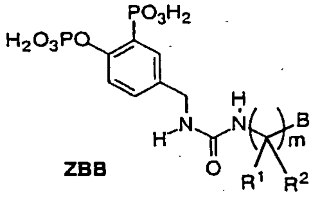

ZAY

Compounds such as Compounds ZAW-ZAY can be prepared according to General Method ZA with appropriate modifications as shown in the scheme below.

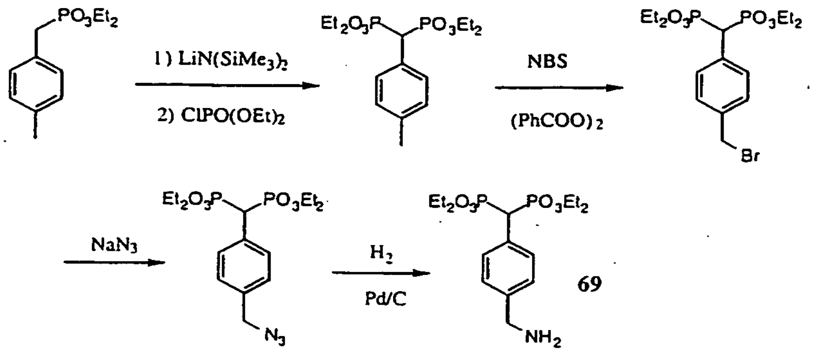

ZAX
1. LiOH•H₂O
2. typical amine, standard coupling conditions
3. Tf₂NPh
4. standard deprotection methods
66
1. LiOH•H₂O
2. typical amine, standard coupling conditions
3. standard deprotection methods
ZAW
1. LiOH•H₂O
2. typical amine, standard coupling conditions
3. BrCH₂CN
4. NaN₃
5. standard deprotection methods
ZAY

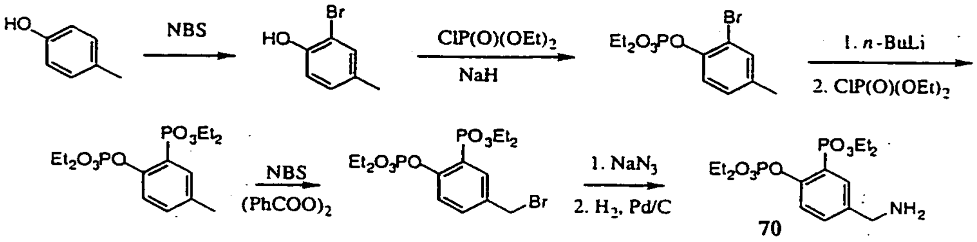
General Method ZE: Preparation of ureido phosphonates


ZBA

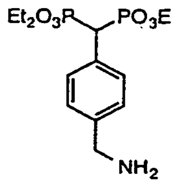

ZBB

Compounds such as Compounds ZBA and ZBB can be prepared according to General Methods M and MA, substituting the appropriate amines (**69**, **70**), which can be prepared according to the scheme below.





Preparation of amine **69**



69

(a) [(4-Methylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester

Diethyl 4-methylbenzylphosphonate (4.55 g, 18.8 mmol) was dissolved in 150 mL dry DME under N_2 and cooled to -42 °C. LiHDMS (1.0 M in THF, 56.5 mL, 56.5 mmol) was added via syringe, and the mixture was stirred at -42 °C for 15 min. Diethyl chlorophosphate (5.5 mL, 37.7 mmol) was then added. The reaction was slowly warmed to 0 °C and stirred for 20 min. The reaction was quenched by 4 N HCl and extracted with DCM (3 times 500 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was distilled using a Kugelrohr apparatus to give pure product as a clear oil (7.0 g, 98%).

(b) [(4-Bromomethylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester

[(4-Methylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester (1.92 g, 5.1 mmol) was dissolved in 20 mL CCl_4 with NBS (1.0 g, 5.6 mmol) and benzoyl peroxide (48 mg, 0.2 mmol). The reaction mixture was refluxed for 2 h. The solid was filtered off and the filtrate was concentrated. The residue was further purified by flash column chromatography over silica gel (EtOAc/MeOH 10:0.5, $R_f = 0.41$) to give 1.8 g (77%) of an oil.

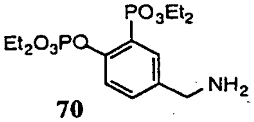
(c) [(4-Azidomethylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester

To 3.4 mL of a 0.5 M NaN_3/DMSO solution (1.71 mmol) at rt was added [(4-bromomethylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester (0.71 g, 1.55 mmol). The reaction mixture was stirred at rt for 2 h and then quenched with 8 mL of H_2O. The reaction was extracted with ether and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave crude product (0.47 g, 72%).

(d) [(4-Aminomethylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester

[(4-Azidomethylphenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester (1.02 g, 2.43 mmol) was dissolved in 15 mL EtOAc. Next, 120 mg Pd/C (10%) was added. The reaction mixture was hydrogenated under 50 psi H_2 for 2 h. After removal of the solid, the solvent was removed to give 0.95 g (100%) of the title product (**69**).

Preparation of amine **70**



70

(e) 2-Bromo-4-methyl phenol

p-Cresol (5.4 g, 50 mmol) was dissolved in 120 mL of MeCN, and NBS (7 g, 39 mmol) was added. The reaction was stirred at rt for 2 h. The precipitate was removed by filtration and the filtrate concentrated. The residue was further purified by flash column chromatography (DCM/hexane 1:3, $R_f = 0.26$) to give the title product as a clear oil (5.3 g, 72%).

(f) Phosphoric acid 2-bromo-4-methyl-phenyl ester diethyl ester

This compound can be prepared according to the method described in General Method ZB (a).

(g) [2-(Diethoxy-phosphoryloxy)-5-methyl-phenyl]-phosphonic acid diethyl ester

Phosphoric acid 2-bromo-4-methyl-phenyl ester diethyl ester (646 mg, 2 mmol) was dissolved in dry ether (10 mL) at 0 °C. *n*-BuLi (1.6 M in hexane, 1.25 mL, 2 mmol) was added dropwise via syringe. The mixture was stirred at 0 °C for 1 h, when diethyl chlorophosphate (0.35 mL, 2.4 mmol) was added. The reaction mixture was stirred at rt overnight and then partitioned between EtOAc and H_2O. The organic layer was separated, washed with 4 N NaOH and brine, and dried over Na_2SO_4. Removal of the solvent resulted in the crude product as a clear oil (0.71 g, 93%).

(h) [2-(Diethoxy-phosphoryloxy)-5-bromomethyl-phenyl]-phosphonic acid diethyl ester

This compound can be prepared according to the method described in General Method ZE (b).

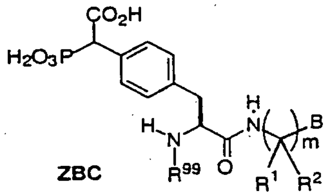
(i) [2-(Diethoxy-phosphoryloxy)-5-azidomethyl-phenyl]-phosphonic acid diethyl ester

This compound can be prepared according to the method described in General Method ZE (c).

(j) [2-(Diethoxy-phosphoryloxy)-5-aminomethyl-phenyl]-phosphonic acid diethyl ester

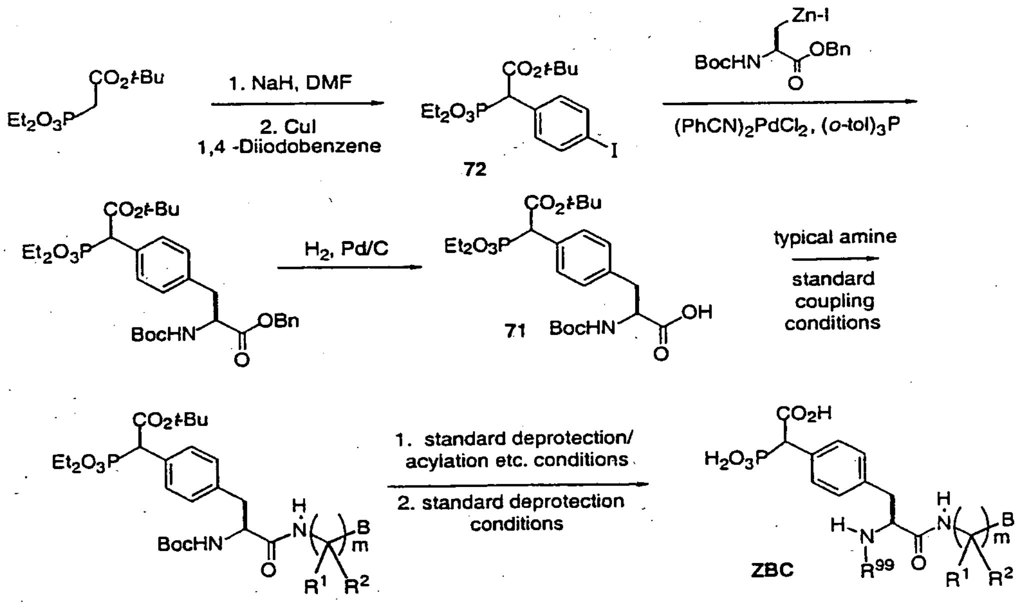
This compound can be prepared according to the method described in General Method ZE (d).

General Method ZF: Preparation of acid phosphonate derivatives

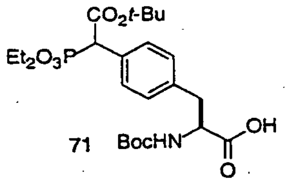


ZBC

Compounds such as Compounds **ZBC** can be prepared according to the scheme below using the appropriate acid coupling partner (**71**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

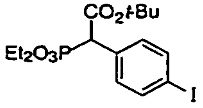

1. NaH, DMF
2. CuI
1,4 -Diiodobenzene
72
(PhCN)2PdCl2, (o-tol)3P
H2, Pd/C
71
typical amine
standard coupling conditions
1. standard deprotection/ acylation etc. conditions
2. standard deprotection conditions
ZBC

Preparation of acid coupling partner **71**



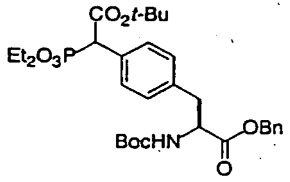
71

(a) Diethoxy-phosphoryl-(4-iodophenyl)acetic acid t-butyl ester (72)



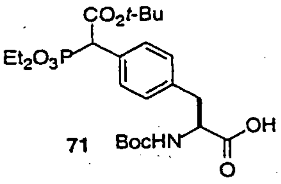
To diethoxyphosphoryl acetic acid *t*-butyl ester (5.04 g, 20 mmol) in DMF (25 mL) was added sodium hydride (0.84 g, 60 mmol) in small portions under nitrogen. After 30 min, a solution of 1,4-diiodobenzene (3.3 g, 10 mmol) and copper(I) iodide (3.8 g, 10 mmol) in DMF (10 mL) was added, and nitrogen was bubbled through this solution for 10 min. The tube was sealed and heated to 100 °C for 6 h. After cooling, the reaction mixture was poured into 10% hydrochloric acid (200 mL). The solution was filtered through Celite and the Celite was repeatedly washed with ethyl acetate (3 x 50 mL). The ethyl acetate layer was separated and the aqueous solution was extracted with ethyl acetate (2 x 25 mL). The combined ethyl acetate extracts were washed with water (10 mL), dried (Na_2SO_4) and concentrated to give a yellow gum, which was purified by column chromatography on silica gel. Elution with hexane/acetone (7/3) to gave a pale yellow gum which, solidified during storage in the freezer. mp 68 °C (3.28 g, 72%).

(b) 4-{(t-butoxycarbonyl-diethoxyphophonyl)-methyl-N-(t-butoxycarbonyl-S-phenyl alanine benzyl ester



Zinc (0.1438 g, 2.2 mmol) was covered with THF/DMA (2 mL) and heated to 60 °C. 1,2-dibromoethane (0.022 mL) was added and the flask was removed from the oil bath. TMS chloride (0.030 mL) was added, and the mixture was sonicated at rt for 15 min after which it was again heated to 60 °C in an oil bath. N-*t*-butoxycarbonyl-2-iodo-L-alanine benzyl ester (0.8105 g, 2 mmol) in THF/DMA (4 mL, 1/1) was added to the activated zinc at 60 °C and the reaction mixture was again sonicated for 30 min after which it was heated to 60 °C. After 1h, a mixture of diethoxy-phosphoryl)-(4-iodophenyl)acetic acid *t*-butyl ester (0.4542 g, 1 mmol) bis(benzonitrile) palladium (II) chloride (21.86 mg, 0.057 mmol) and tri-o-tolylphosphine (33.17 mg, 0.109 mmol) in THF/DMA (8 mL, 1/1) was added and the reaction mixture was heated to 60 °C for 1 h, then diluted with excess ethyl acetate (~200 mL) and 1N HCl (20 mL) and the resulting mixture was filtered through Celite. The organic layer was separated, washed (water, 10 mL) , dried (Na_2SO_4) and concentrated in vacuo. The resulting gum was purified by flash chromatography over silica gel using hexane/ethyl acetate (85/15) to give recovered starting material (120 mg, 22%), and the product (424 mg, 70%). mp 89 °C.

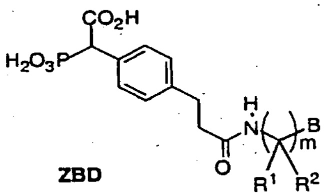
(c) 4-{(t-butoxycarbonyl-diethoxyphophonyl)-methyl-N-(t-butoxycarbonyl)-S-phenyl alanine (**71**)



71

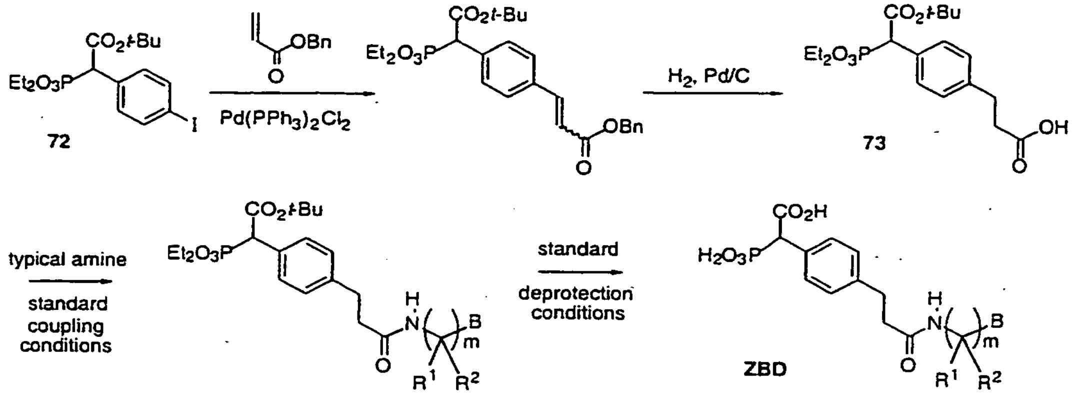
To 4-{(t-butoxycarbonyl-diethoxyphophonyl)-methyl-N-(t-butoxycarbonyl-S-phenyl alanine benzyl ester (420 mg, 0.695 mmol) was added ethyl acetate (45 mL) followed by 10% Pd/C (75 mg) carefully in an inert atmosphere. The flask was fitted with a balloon containing hydrogen and stirred at rt for 5 h. The reaction mixture was filtered through a pad of Celite, which was washed with ethyl acetate (3 x 10 mL). The combined filtrate was concentrated to give 348.2 mg (97%). mp 138 °C.

General Method ZG: Preparation of hydrocinnamic acid derivatives

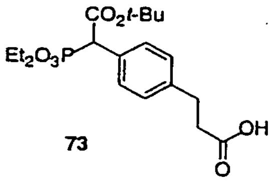


ZBD

Compounds such as Compounds **ZBD** can be prepared according to the scheme below using the appropriate acid coupling partner (**73**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

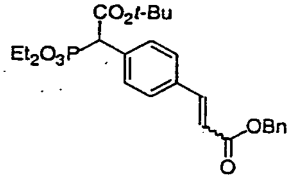


Preparation of acid coupling partner **73**



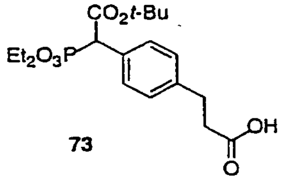
73

(a) 3-(4-tert-butoxycarbonyl-(diethoxyphosphonyl)-methyl-phenyl-)-acrylic acid benzyl ester



To diethoxy-phosphoryl-(4-iodophenyl)acetic acid *t*-butyl ester (72) (500 mg, 1.76 mmol) was added benzyl acrylate (589 mg, 3.52 mmol), $Pd(PPh_3)_2Cl_2$ (81.5 mg, 0.106 mmol) followed by triethylamine (0.740 mL, 5.28 mmol). This mixture was heated to 70 °C under nitrogen for 4 h. The reaction mixture was diluted with excess ethyl acetate and water and filtered through a pad of Celite. The ethyl acetate layer was separated, washed (water, 5 mL), dried (Na_2SO_4) and concentrated. The resulting gum was purified by column chromatography over silica gel using hexane/acetone (25%) to give a yellow liquid (449 mg, 65%) which is a mixture of E and Z isomers, which was used as such in the next step. Electrospray MS: 489 (M+H).

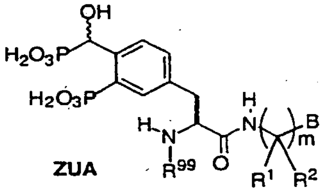
(b) 3-(4-tert-butoxycarbonyl-(diethoxyphosphonyl)-methyl-phenyl-)propionic acid (73)



73

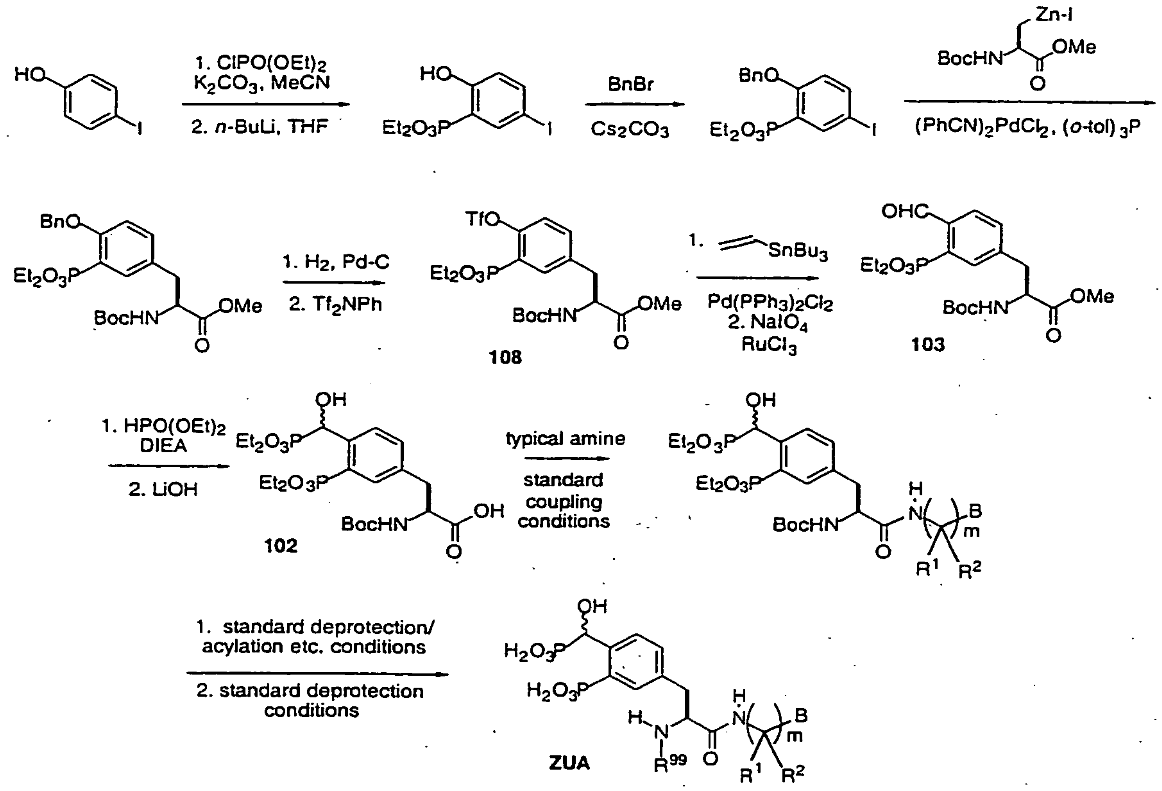
Title compound was hydrogenolyzed using the same conditions used in General Method ZF (c) above. Glassy gum. Electrospray MS: 401 (M+H)

General Method ZH: Preparation of hydroxy phosphonate derivatives

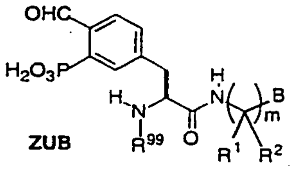


ZUA

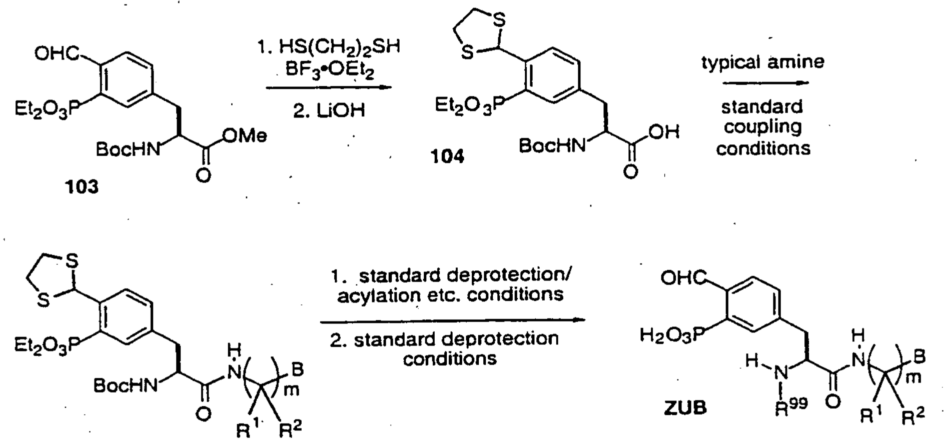
Compounds such as Compounds **ZUA** can be prepared according to the scheme below using the appropriate acid coupling partner (**102**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.



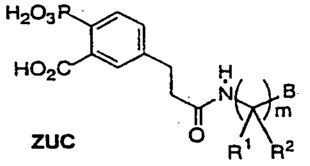
General Method ZI: Preparation of aldehyde phosphonate derivatives


ZUB

Compounds such as Compounds **ZUB** can be prepared according to the scheme below using the appropriate acid coupling partner (**104**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

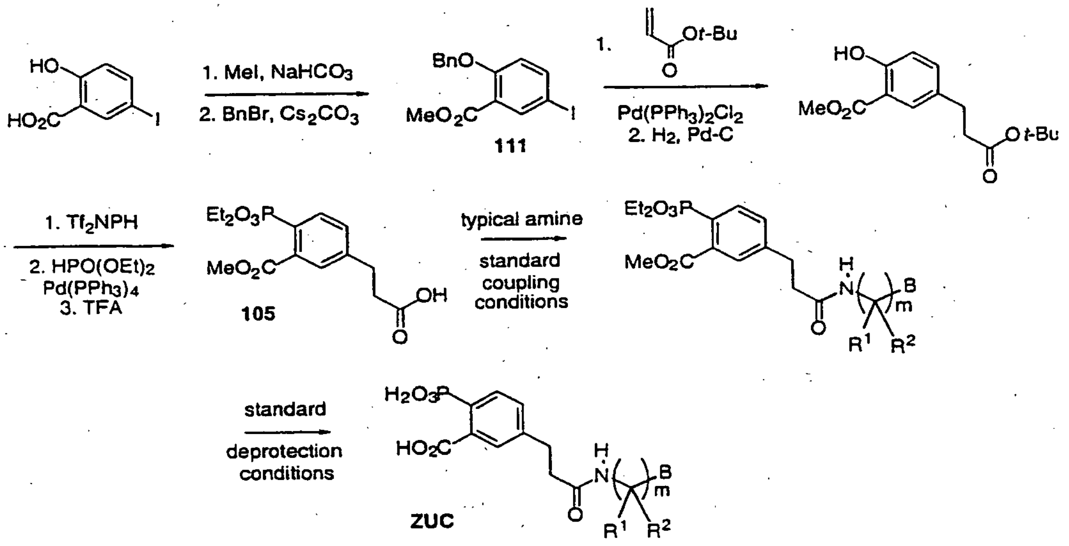


General Method ZJ: Preparation of hydrocinnamic acid derivatives

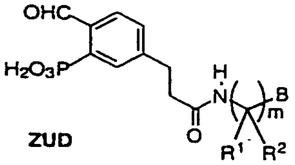


ZUC

Compounds such as Compounds **ZUC** can be prepared according to the scheme below using the appropriate acid coupling partner (**105**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

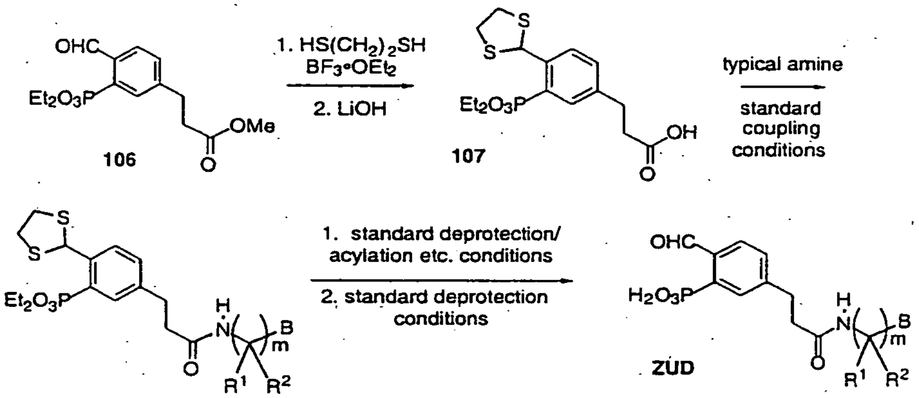


General Method ZK: Preparation of hydrocinnamic acid derivatives

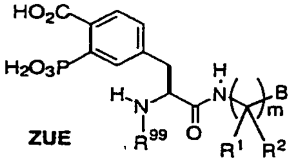


ZUD

Compounds such as Compounds **ZUD** can be prepared according to the scheme below using the appropriate acid coupling partner (**107**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

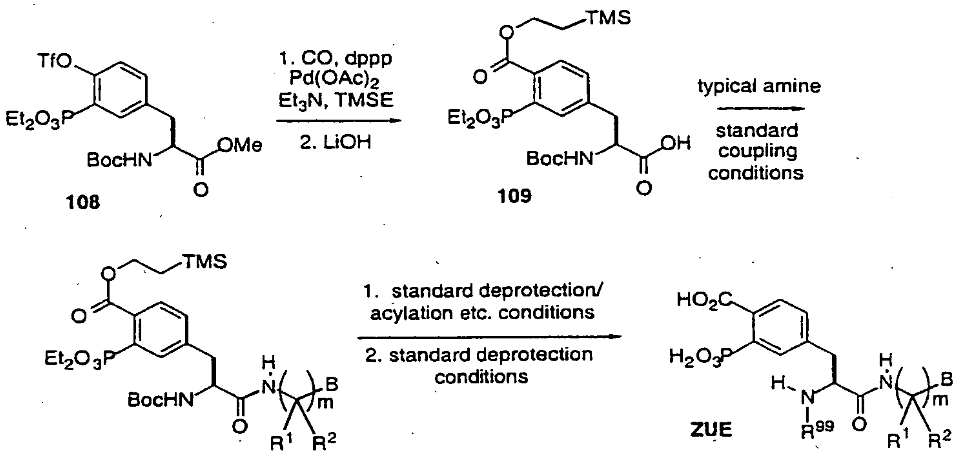

OHC
Et2O3P
OMe
O
106
1. HS(CH2)2SH
BF3•OEt2
2. LiOH
S
S
Et2O3P
OH
O
107
typical amine
standard coupling conditions
S
S
Et2O3P
H
N
B
m
O
R1
R2
1. standard deprotection/ acylation etc. conditions
2. standard deprotection conditions
OHC
H2O3P
H
N
B
m
ZUD
O
R1
R2

General Method ZL: Preparation of acid phosphonate derivatives

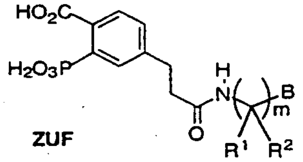


ZUE

Compounds such as Compounds **ZUE** can be prepared according to the scheme below using the appropriate acid coupling partner (**109**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E. F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

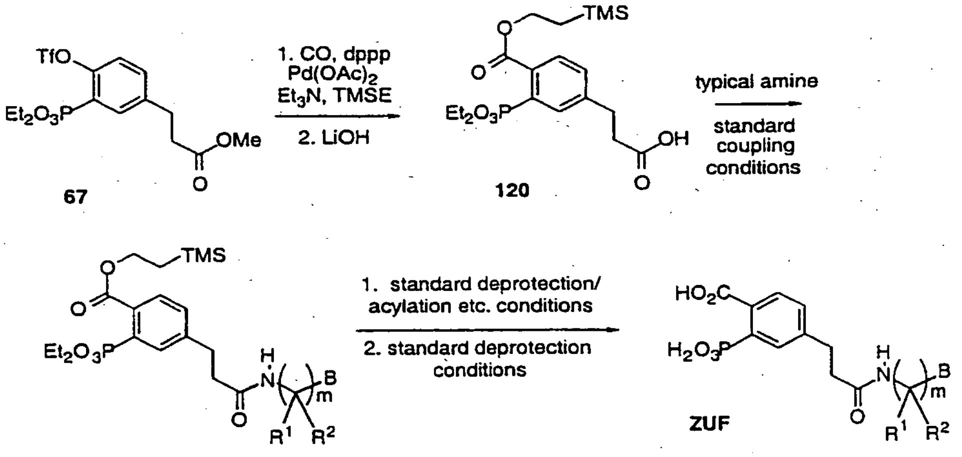


General Method ZM: Preparation of hydrocinnamic acid derivatives

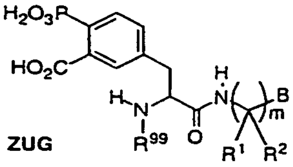


ZUF

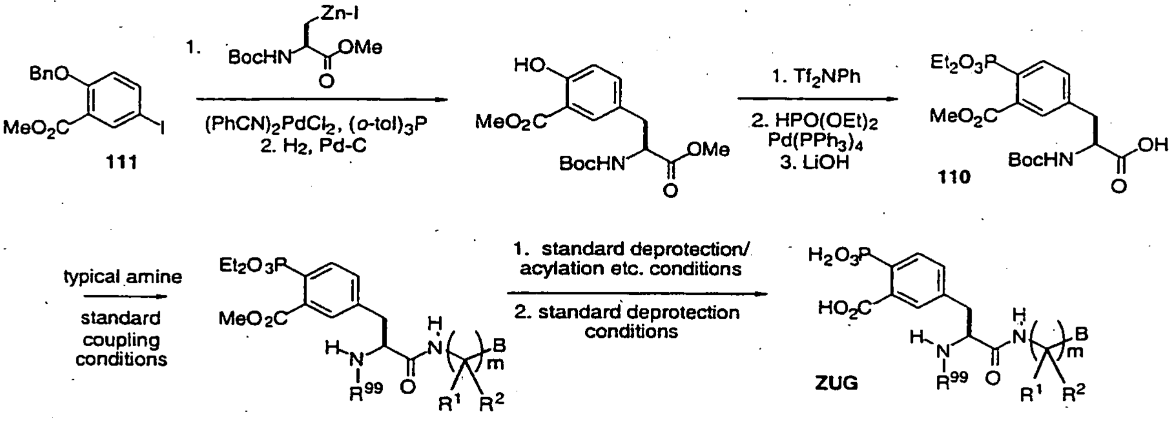
Compounds such as Compounds **ZUF** can be prepared according to the scheme below using the appropriate acid coupling partner (**120**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.



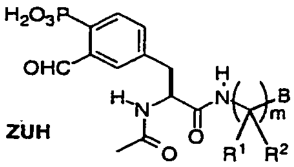
General Method ZN: Preparation of acid phosphonate derivatives


ZUG

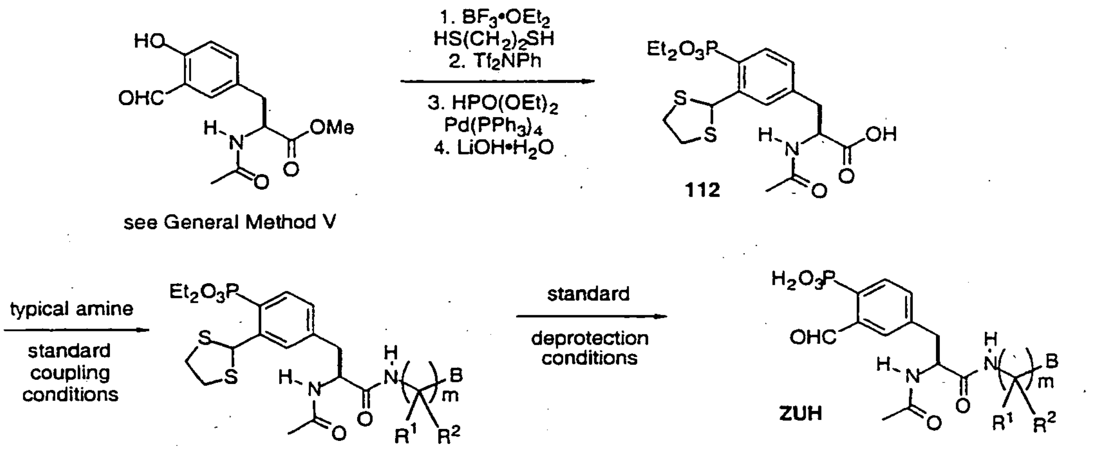
Compounds such as Compounds **ZUG** can be prepared according to the scheme below using the appropriate acid coupling partner **(110)** along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.



General Method ZO: Preparation of aldehyde phosphonate derivatives


ZUH

Compounds such as Compounds **ZUH** can be prepared according to the scheme below using the appropriate acid coupling partner **(112)** along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

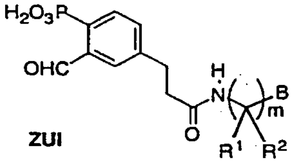


see General Method V

112

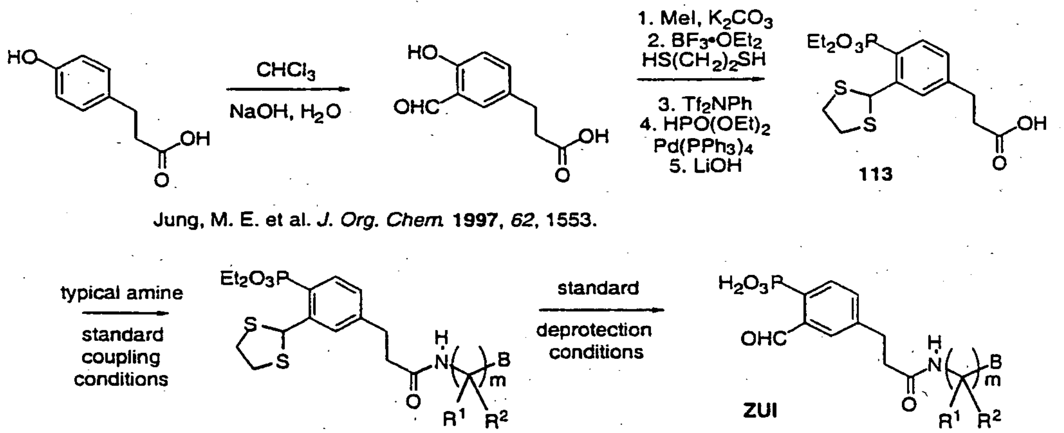
ZUH

General Method ZP: Preparation of hydrocinnamic acid derivatives



ZUI

Compounds such as Compounds **ZUI** can be prepared according to the scheme below using the appropriate acid coupling partner (**113**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in proecting group strategies.

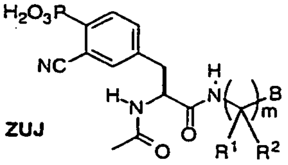


Jung, M. E. et al. *J. Org. Chem.* **1997**, *62*, 1553.

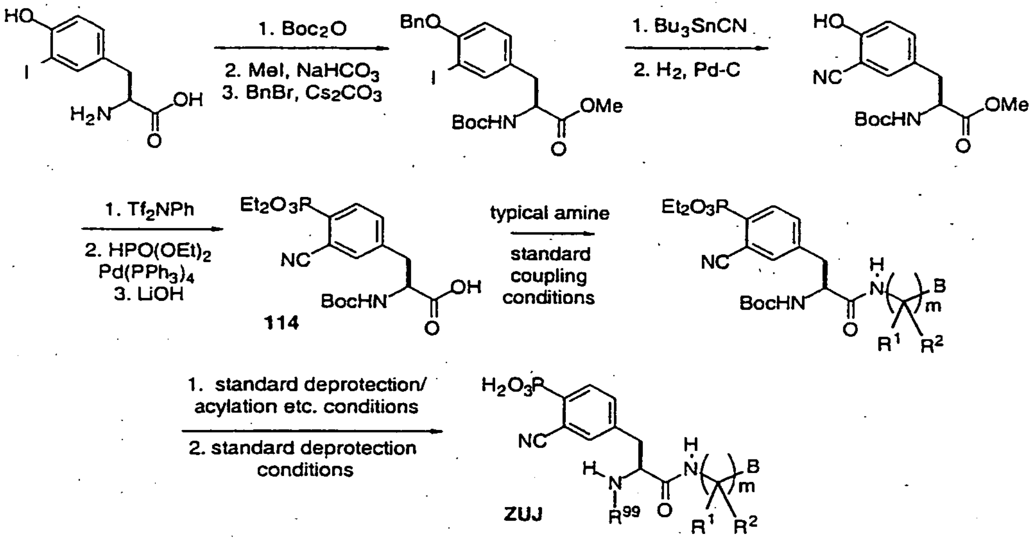
113

ZUI

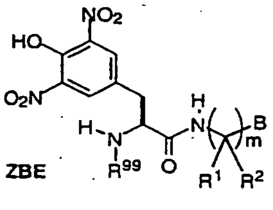
General Method ZQ: Preparation of cyano phosphonate derivatives

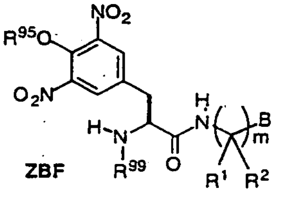

ZUJ

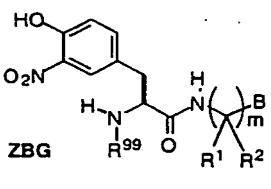
Compounds such as Compounds **ZUJ** can be prepared according to the scheme below using the appropriate acid coupling partner (**114**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G, for example. This method is analogous to Coupling Conditions C and D with obvious differences in protecting group strategies.

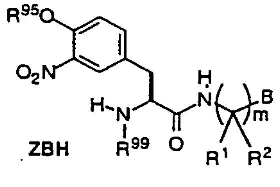


General Method ZR: Preparation of nitro or dinitro tyrosine derivatives

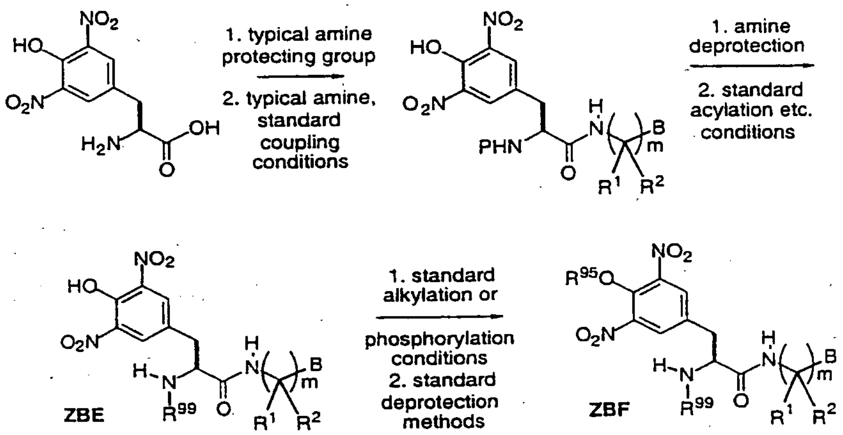

ZBE


ZBF

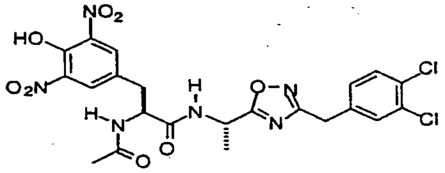

ZBG


ZBH

Compounds such as Compounds ZBE, ZBF, ZBG and ZBH (R^{95} = $-PO_3H_2$, $-CH_2CO_2H$, $-CH_2PO_3H_2$, for example) can be prepared according to Coupling Conditions C and D as shown in the scheme below (for the N-Ac dinitro example), using the appropriate acid coupling partner along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G. This method is similar to General Methods N and WD.


NO2
HO
O2N
H2N
OH
O
1. typical amine protecting group
2. typical amine, standard coupling conditions
PHN
H
N
B
m
R1 R2
1. amine deprotection
2. standard acylation etc. conditions
ZBE
R99
1. standard alkylation or phosphorylation conditions
2. standard deprotection methods
R95O
ZBF

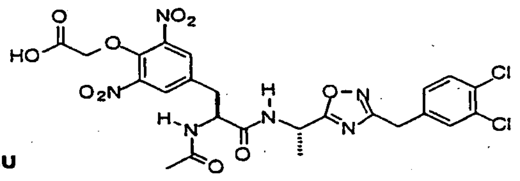
76. Compound ZBT



ZBT

Compounds such as Compound ZBT can be prepared according to General Method ZR. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 565 (M-H).

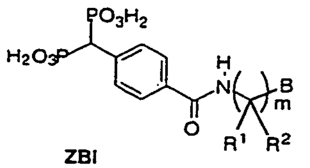
77. Compound ZBU



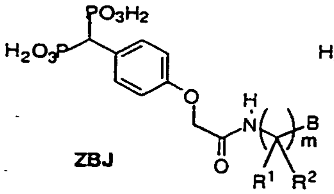
ZBU

Compounds such as Compound ZBU can be prepared according to General Method ZR. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 625 (M+H).

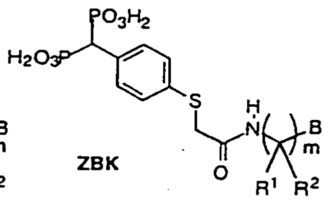
General Method ZS: Preparation of other phosphonate derivatives



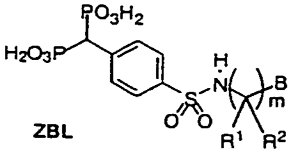
ZBI



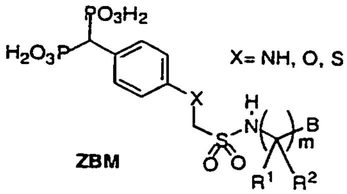
ZBJ



ZBK

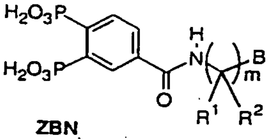


ZBL



X= NH, O, S

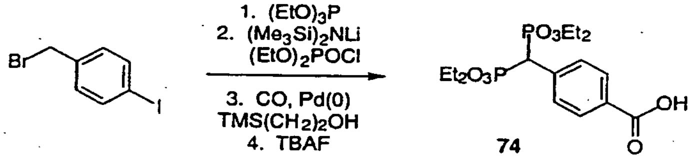
ZBM



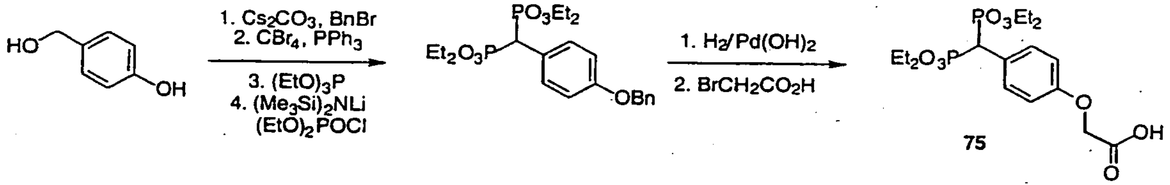
ZBN

Compounds such as Compounds ZBI-ZBN can be prepared according to General Method X using the appropriate acid coupling partner (**74** - **79**) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G.

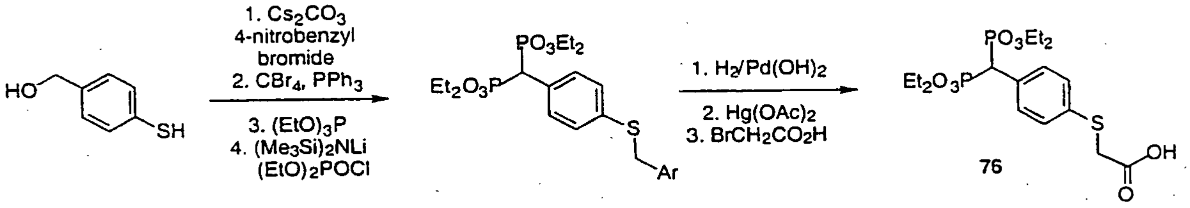
Preparation of Acid **74**



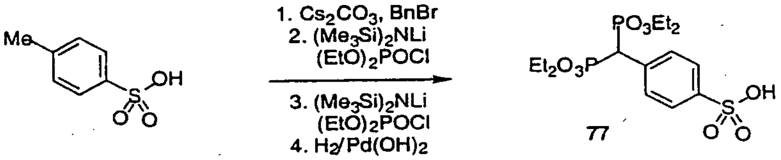
Preparation of Acid **75**



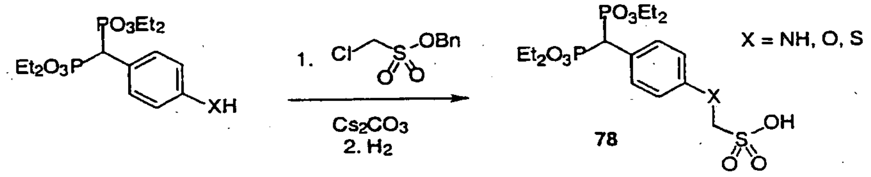
Preparation of Acid **76**



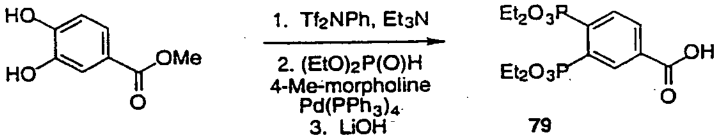
Preparation of Acid **77**



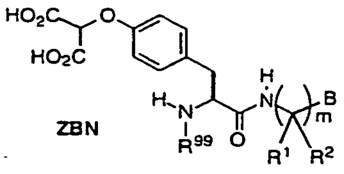
Preparation of Acid **78**

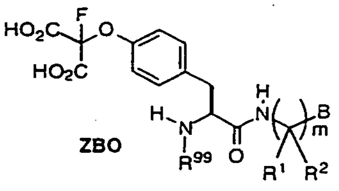


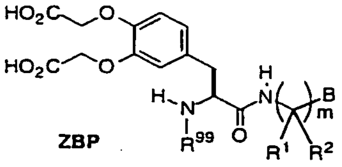
Preparation of Acid **79**

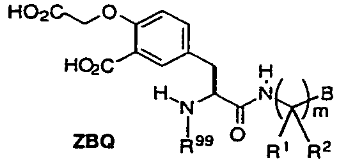


General Method ZT: Preparation of Misc. Acid analogs


ZBN


ZBO


ZBP


ZBQ

Compounds such as Compounds ZBN, ZBO, ZBP and ZBQ can be prepared according to Coupling Conditions C and D using the appropriate acid coupling partner, which can be prepared according to literature methods (Burke, T. R., Jr. et al. *Tetrahedron* **1998**, *54*, 9981 and references cited therein) along with the appropriate amine coupling partner, which can be prepared according to General Methods A, B, E, F and G.

Inhibition of Binding to Src SH2:

The binding affinities of compounds of the present invention to Src SH2 can be determined according to the method of Lynch et al. PCT/US97/06746. The following representative compounds of the present invention were determined to have an IC50 less than 50 micromolar: Compound A, Compound L, Compound V, Compound Z, Compound AB, Compound ZAA, Compound ZAB, Compound BA, Compound CP, Compound EF, Compound EU, Compound BF and Compound EW.

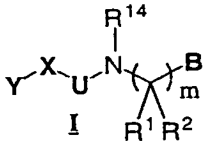
Inhibition of Binding to Zap-70 SH2:

The binding affinities of compounds of the present invention to Zap-70 SH2 can be determined according to the method of Lynch et al. PCT/US97/06746. The following representative compounds of the present invention were determined to have an IC50 less than 50 micromolar: Compound FH, Compound FW, Compound FY, Compound FE, Compound FAI, Compound FAW, Compound FAZ, Compound FBB, Compound OA, Compound OL, Compound OK, Compound ON, Compound OQ and Compound AE.

◆ ◆ ◆ ◆

Claims

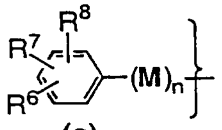
1. A compound of the formula:



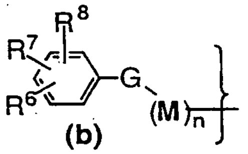
I

wherein

Y is

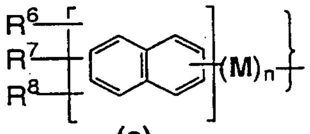


(a)



(b)

or



(c)

G is –O–, –S– or –NR–;

$\mathbf{R^6}$ comprises –OR, $-\mathrm{APO_3RR'}$, $-\mathrm{OPO_3RR'}$, $-\mathrm{ASO_3R}$, $-\mathrm{OSO_3R}$, $-\mathrm{ACO_2R}$, –A-tetrazole, $-\mathrm{ASO_2NRR'}$, $-\mathrm{ACOCF_3}$, –C(O)J, –C(R)(J)(K) or –C(Z)(J)(K);

where each occurrence of **A** is independently a covalent bond, –G–M– or $-(\mathrm{M})_m-$;

each occurrence of **M** is an independently selected, substituted or unsubstituted, methylene moiety, and any M-M' moiety may be electronically saturated or unsaturated;

each **n** is independently 0, 1, 2, 3, 4 or 5;

each **m** is independently 0, 1 or 2;

J and **K** are independently $-\mathrm{APO_3RR'}$, $-\mathrm{OPO_3RR'}$, $-\mathrm{ASO_3R}$, $-\mathrm{OSO_3R}$, $-\mathrm{ACO_2R}$, –A–tetrazole, $-\mathrm{ASO_2NRR'}$, $-(\mathrm{M})_n-\mathrm{NRR'}$ or $-(\mathrm{M})_n-\mathrm{OR}$;

Z is a halogen;

$\mathbf{R^7}$ and $\mathbf{R^8}$ are independently **R**, –CN, $-\mathrm{NO_2}$, **Z**, **J**, $-\mathrm{A(M)_n}$aliphatic, $-\mathrm{G(M)_n}$aliphatic, $-(\mathrm{M})_n\mathrm{COCF_3}$, $-(\mathrm{M})_n\mathrm{OH}$, $-(\mathrm{M})_n\mathrm{COOR}$, $-\mathrm{A}-(\mathrm{M})_n\mathrm{NRR'}$, $-\mathrm{G(M)_qNRR'}$, $-(\mathrm{M})_n\mathrm{CHO}$, $-\mathrm{A(M)_nN(R)(CO)R'}$, $-\mathrm{A(M)_nN(R)(CO)GR'}$, $-\mathrm{G(M)_qN(R)(CO)R'}$,

$-G-(M)_qN(R)(CO)G'R'$, $-A-(M)_n-CO-NRR'$, or $-G(M)_n-CO-NRR'$, where the aliphatic groups may be substituted or unsubstituted; or R^7 is a covalent bond to an R^4 substituent of X to form an aliphatic, aryl or heterocyclic ring of 4 to 8 atoms; additionally, R^7 and R^8 may be of the structure -(C=O)**R** so long as R is not alkenyl or alkynyl or **B** is not a thiazole.

each occurrence of **R** (unnumbered) represents hydrogen or an aliphatic, heteroaliphatic, aryl, heteroaryl, (aryl)aliphatic–, or (heteroaryl)aliphatic– moiety, each of which (other than hydrogen) may be substituted or unsubstituted;

q is an integer from 1 to 8;

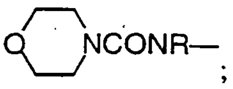
R^1 is hydrogen, aliphatic,$-(M)_n-$cycloaliphatic, $-(M)_n-$aryl, or $-(M)_n-$heterocyclic, each of which, other than H, may be substituted or unsubstituted; and R^2 is hydrogen or substituted or unsubstituted aliphatic;

or R^1 and R^2 are covalently linked together to form a ring;

or R^1 or R^2 are covalently linked either to **B** or a substituent of **B** to form a 4 - 10-membered, saturated or unsaturated, ring, or to the N depicted in Formula I above to form a 5, 6 or 7-membered, saturated or unsaturated, ring;

X is: $-(CR^3R^4)_m-$ or $-NR^4-$;

R^3 is hydrogen, R(CO)NR'–, **RR'**N(CO)NR''–, R'SO_2NR–, R'CSNR–, **RR''**NCSNR''–, **RR''**NSO_2NR''–, R'OCONR–, RR'N–, or



;

R^4 is hydrogen, aliphatic, cycloaliphatic–$(M)_n$–, aryl–$(M)_n$–, heterocyclic–$(M)_n$–, R–SO_2M_n– , (RO-CO)$(M)_n$– or (RR'N-CO)$(M)_n$–, where the aliphatic, cycloaliphatic, aryl or heterocyclic moiety is substituted or unsubstituted;

B is –{**HET**]$R^9R^{10}R^{11}R^{12}$, where **HET** is a heterocyclic moiety;

R^9, R^{10} and R^{11} are independently $-(M)_nZ$, $-(M)_nR$, $-(M)_nGR$, $-(M)_nWR$, or $-(M)_nWGR$;

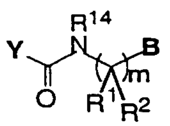
R^{12} is independently selected from $-(M)_qZ$, $-(M)_nR$, $-(M)_qGR$, $-(M)_nWR$, and $-(M)_nWGR$;

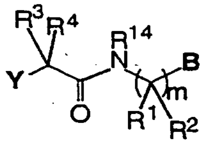
R^{14} is R; and,

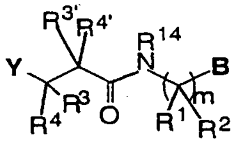
U and **W** are independently –CO–, –CS–, –M–, –SO–, or –SO_2–;

or a pharmaceutically acceptable derivative thereof.

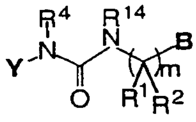
2. A compound of claim 1 of the formula:







or



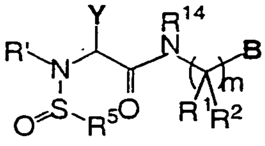
3. A compound of claim 2 containing a R^4 moiety which is H.

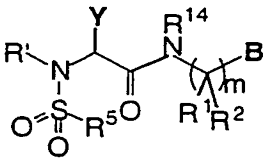
4. A compound of claim 2 in which R^3 and R^4 are H.

5. A compound of claim 1 or 2 wherein n is 0, 1 or 2.

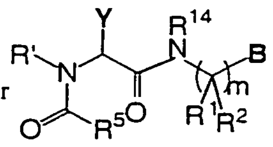
6. A compound of claim 1 wherein **X** is –CH(NH_2)–.

7. A compound of claim 1 of the formula





or



where R^5 comprises a substituted or unsubstituted lower aliphatic or alkoxyl or is a substituted or unsubstituted $-(M)_n-$aryl or $-(M)_n-$heterocyclic group.

8. A compound of claim 7 wherein R^5 comprises $-(M)_nCH_3$, $-(M)_n$aryl, $-(M)_n$heterocyclic, $-(M)_nCN$ or $-(M)_nCOOR$, where n is 0, 1, 2, 3, 4, or 5.

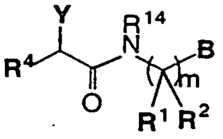
9. A compound of claim 7 wherein R^5 is a methyl, ethyl, propyl, butyl, pentyl, hexyl, benzyl, aryl, heterocyclic, $-(CH_2)$aryl or $-(CH_2)$heterocyclic moiety, which may be substituted or unsubstituted.

10. A compound of claim 7 wherein R^5 comprises $-(CH_2)_nCH_3$, $-(CH_2)(CH_2)_n$aryl, $-(CH_2)(CH_2)_n$heterocyclic, $-(CH_2)(CH_2)_nCN$, or $-(CH_2)(CH_2)_nCOOR$, where n is 0, 1, 2, 3, 4, or 5.

11. A compound of claim 10 wherein R^5 comprises $-CH_2CN$, $-(CH_2)COOR$, $-(CH_2)_2COOR$, $-(CH_2)_3COOR$, $-(CH_2)_4COOR$, where R is H, lower alkyl or benzyl.

12. A compound of claim 10 wherein R^5 comprises $-O-$(substituted or unsubstituted lower alkyl or benzyl).

13. A compound of claim 1 of the formula



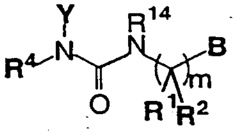
where $\mathbf{R}^4$ is hydrogen, substituted or unsubstituted aliphatic (which may be branched, unbranched or cyclic), substituted or unsubstituted aryl–$(\mathbf{M})_n$–, substituted or unsubstituted heterocyclic–$(\mathbf{M})_n$–, or $(CO_2R)(\mathbf{M})_n$–.

14. A compound of claim 13 wherein $\mathbf{R}^4$ is –$(\mathbf{M})_n$(CO)OR, –$(\mathbf{M})_n SO_2R$, –$(\mathbf{M})_n$(CO)N**RR'**, or –$(\mathbf{M})_n$(tetrazole).

15. A compound of claim 14 wherein $\mathbf{R}^4$ is –CH_2COOR, –CH_2SO_2R, –CH_2(CO)N**RR'**, or –tetrazole.

16. A compound of claim 14 wherein each R and R' is independently H, lower alkyl or benzyl.

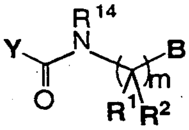
17. A compound of claim 1 of the formula



where $\mathbf{R}^4$ is hydrogen, substituted or unsubstituted aliphatic (which may be branched, unbranched or cyclic), substituted or unsubstituted aryl–$(\mathbf{M})_n$–, substituted or unsubstituted heterocyclic–$(\mathbf{M})_n$–, or $(CO_2R)(\mathbf{M})_n$–.

18. A compound of claim 17 wherein $\mathbf{R}^4$ is hydrogen.

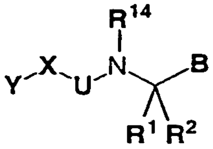
19. A compound of claim 1 of the formula



20. A compound of any of claims 7 – 12 wherein R and R' are H.

21. A compound of any of claims 1 – 20 wherein R^{14} is H.

22. A compound of any of claims 1 – 21, having the formula:

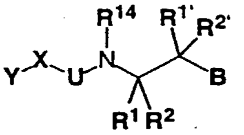


wherein $\mathbf{R}^1$ is H, and $\mathbf{R}^2$ comprises H, $-(\mathbf{M})_n\mathrm{H}$, $-(\mathbf{M})_n-$(substituted or unsubstituted lower alkyl), $-(\mathbf{M})_n-$(substituted or unsubstituted aryl), $-(\mathbf{M})_n-$(substituted or unsubstituted heterocyclic), $-(\mathbf{M})_n-\mathrm{COOR}$, or $-(\mathbf{M})_n(\mathrm{CO})\mathrm{N}\mathbf{RR}'$.

23. A compound of claim 22, wherein $\mathbf{R}^2$ is methyl, ethyl, i–propyl, n–propyl, n–butyl, isobutyl, n–amyl, sec–amyl, isoamyl, substituted benzyl, $-CH_2-$(3–indolyl), $-CH_2CH_2COOR$, $-CH_2CH_2CONH_2$, $-CH_2COOR$ or $-CH_2CONH_2$.

24. A compound of claim 1–21, wherein $\mathbf{R}^1$ and $\mathbf{R}^2$ are independently selected, substituted or unsubstituted lower aliphatic groups, or $\mathbf{R}^1$ and $\mathbf{R}^2$ are covalently linked to each other to form a ring.

25. A compound of claim 1 – 21, having the formula



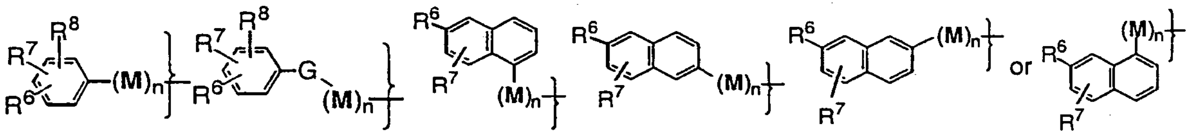
wherein each of $\mathbf{R}^1$, $\mathbf{R}^{1'}$, $\mathbf{R}^2$, and $\mathbf{R}^{2'}$ is independently selected from H, $-(\mathbf{M})_n\mathrm{H}$, $-(\mathbf{M})_n-$(substituted or unsubstituted lower alkyl), $-(\mathbf{M})_n-$(substituted or unsubstituted aryl), $-(\mathbf{M})_n-$(substituted or unsubstituted heterocyclic), $-(\mathbf{M})_n-\mathrm{COOR}$ and $-(\mathbf{M})_n(\mathrm{CO})\mathrm{N}\mathbf{RR}'$.

26. A compound of claim 25, wherein each of $\mathbf{R}^1$, $\mathbf{R}^{1'}$, $\mathbf{R}^2$, and $\mathbf{R}^{2'}$ is H.

27. A compound of claim 1 – 24, wherein at least one of $\mathbf{R}^1$ and $\mathbf{R}^2$ is methyl, ethyl, i–propyl, n–propyl, n–butyl, isobutyl, t-butyl, n–amyl, sec–amyl, isoamyl, substituted benzyl, $-CH_2$–(3–indolyl), $-CH_2CH_2COOR$, $-CH_2CH_2CONH_2$, $-CH_2COOR$ or $-CH_2CONRR'$, or $\mathbf{R}^1$ and $\mathbf{R}^2$ are covalently linked to form a ring.

28. A compound of claim 25, wherein at least one of $\mathbf{R}^1$, $\mathbf{R}^{1'}$, $\mathbf{R}^2$, and $\mathbf{R}^{2'}$ is methyl, ethyl, i–propyl, n–propyl, n–butyl, isobutyl, t-butyl, n–amyl, sec–amyl, isoamyl, substituted benzyl, $-CH_2$–(3–indolyl), $-CH_2CH_2COOR$, $-CH_2CH_2CONH_2$, $-CH_2COOR$ or $-CH_2CONRR'$, or two of $\mathbf{R}^1$, $\mathbf{R}^{1'}$, $\mathbf{R}^2$, and $\mathbf{R}^{2'}$ are covalently linked to form a ring.

29. A compound of any of claims 1 – 28, wherein Y comprises



30. A compound of claim 29 wherein

$\mathbf{R}^6$ comprises $-OR$, $-APO_3RR'$, $-OPO_3RR'$, $-ASO_3R$, $-OSO_3R$, $-ACO_2R$, –A-tetrazole, $-ASO_2NRR'$, $-ACOCF_3$, $-C(R)(J)(K)$ or $-C(Z)(J)(K)$; and

$\mathbf{R}^7$ and $\mathbf{R}^8$ are independently H, –CN, $-NO_2$, halogen, J, $-A-(M)_n$aliphatic, $-G-(M)_n$aliphatic, $-(M)_nCOCF_3$, $-(M)_nOH$, $-(M)_nCOOR$, $-A-(M)_nNRR'$, $-G-(M)_nNRR'$, $-(M)_nCHO$, $-A-(M)_nN(R)(CO)R'$, $-G-(M)_nN(R)(CO)R'$, $-A-(M)_n-CO-NRR'$, or $-G-(M)_n-CO-NRR'$, where the aliphatic groups may be substituted or unsubstituted; or $\mathbf{R}^7$ is a covalent bond to an $\mathbf{R}^4$ substituent of X to form an aliphatic, aryl or heterocyclic ring of 4 to 8 atoms.

31. A compound of claim 29 wherein

$\mathbf{R}^6$ comprises $-OR$, $-APO_3RR'$, $-OPO_3RR'$, $-ACO_2R$, $-ACOCF_3$ or $-C(R)(J)(K)$;

A comprises $-CH_2-$, $-OCH_2-$, $-CF_2-$, $-CHF-$, $-CHOH-$ or a covalent bond:

each **R** and **R'** is H, or substituted or unsubstituted lower alkyl or substituted or unsubstituted benzyl; and,

$\mathbf{R}^7$ and $\mathbf{R}^8$ are independently H, **J**, $-\mathbf{A}-(\mathbf{M})_n$substituted or unsubstituted aliphatic, $-\mathbf{G}-(\mathbf{M})_n$substituted or unsubstituted aliphatic, $-(M)_nCOCF_3$, $-(M)_nOH$, $-(M)_nCOOR$, $-\mathbf{A}-(\mathbf{M})_n\mathbf{NRR'}$, $-(M)_nCHO$, $-\mathbf{A}-(\mathbf{M})_nN(R)(CO)R'$ or $-\mathbf{A}-(\mathbf{M})_n-CO-\mathbf{NRR'}$.

32. A compound of claim 29 wherein $\mathbf{R}^6$ comprises $-OH$, $-PO_3\mathbf{RR'}$, $-OPO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-\mathbf{N}RCH_2CO_2\mathbf{R'}$, $-N(CH_2CO_2R)_2$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, $-CF_2SO_3\mathbf{R}$, $-CH_2COCF_3$, $-CF_2COCF_3$, $-CH(PO_3\mathbf{RR'})_2$, $-CH(OH)(PO_3\mathbf{RR'})$, $-CH(NH_2)(PO_3\mathbf{RR'})$, $-CH(CO_2\mathbf{R})_2$, $-CF(CO_2\mathbf{R})_2$, $-CH(PO_3\mathbf{RR'})(CO_2\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_3\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_2NH_2)$, $-CH(SO_2NH_2)_2$, or $-CH(SO_3\mathbf{RR'})_2$.

33. A compound of claim 32 in which one or more of R, R' and R" in the $-PO_3\mathbf{RR'}$, $-OPO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-\mathbf{N}RCH_2CO_2\mathbf{R'}$, $-N(CH_2CO_2R)_2$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, $-CF_2SO_3\mathbf{R}$, $-CH_2COCF_3$, $-CF_2COCF_3$, $-CH(PO_3\mathbf{RR'})_2$, $-CH(OH)(PO_3\mathbf{RR'})$, $-CH(NH_2)(PO_3\mathbf{RR'})$, $-CH(CO_2\mathbf{R})_2$, $-CF(CO_2\mathbf{R})_2$, $-CH(PO_3\mathbf{RR'})(CO_2\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_3\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_2NH_2)$, $-CH(SO_2NH_2)_2$, or $-CH(SO_3\mathbf{RR'})_2$ moiety is H.

34. A compound of claim 32 in which one or more of R, R' and R" in the $-PO_3\mathbf{RR'}$, $-OPO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-\mathbf{N}RCH_2CO_2\mathbf{R'}$, $-N(CH_2CO_2R)_2$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, $-CF_2SO_3\mathbf{R}$, $-CH_2COCF_3$, $-CF_2COCF_3$, $-CH(PO_3\mathbf{RR'})_2$, $-CH(OH)(PO_3\mathbf{RR'})$, $-CH(NH_2)(PO_3\mathbf{RR'})$,

$-CH(CO_2\mathbf{R})_2$, $-CH(PO_3\mathbf{RR'})(CO_2\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_3\mathbf{R''})$, $-CH(PO_3\mathbf{RR'})(SO_2NH_2)$, $-CH(SO_2NH_2)_2$, or $-CH(SO_3\mathbf{RR'})_2$ moiety is $-(M)_mCH_2Z$, $-(M)_mCHZ_2$, $-(M)_mCZ_3$, $-R^{15}$, $-M-O-CO-R^{15}$ or $-M-O-CO-OR^{15}$, where Z is halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic.

35. A compound of claim 34 in which R^{15} is methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl.

36. A compound of claim 32 – 35 wherein $\mathbf{R}^7$ and $\mathbf{R}^8$ are H.

37. A compound of claim 32 – 35 wherein $\mathbf{R}^7$ is **J**, $-\mathbf{A}-(\mathbf{M})_n$(substituted or unsubstituted aliphatic, aryl or heterocyclic), $-\mathbf{G}-(\mathbf{M})_n$(substituted or unsubstituted aliphatic, aryl or heterocyclic), $-(\mathbf{M})_nCOCF_3$, $-(\mathbf{M})_nOH$, $-(\mathbf{M})_nCOOR$, $-\mathbf{A}-(\mathbf{M})_n\mathbf{NRR'}$, $-(\mathbf{M})_nCHO$, $-\mathbf{A}(\mathbf{M})_nN(R)(CO)R'$, $-\mathbf{A}(\mathbf{M})_n\mathbf{NRR'}$ or $-\mathbf{A}-(\mathbf{M})_n-CO-\mathbf{NRR'}$; and $\mathbf{R}^8$ is H.

38. A compound of claim 32 – 35 wherein $\mathbf{R}^7$ is lower alkyl, lower alkenyl, $-OH$, $-NH_2$, $-NO_2$, $-CN$, $-NHR$, $-NHCOR$, $-CHO$, $-CH_2CHO$, $-PO_3\mathbf{RR'}$, $-\mathbf{O}PO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-NHCH_2CO_2\mathbf{R}$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-SO_3R$, $-CH_2SO_3\mathbf{R}$, $-CF_2SO_3\mathbf{R}$, $-COCF_3$, $-COCH_2F$, $-COCF_2H$, $-CF_2COCF_3$ or $-SO_2NH_2$.

39. A compound of claim 38 in which one or both of R and R' in $-PO_3\mathbf{RR'}$, $-\mathbf{O}PO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-NHCH_2CO_2\mathbf{R}$, $-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-SO_3\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, or $-CF_2SO_3\mathbf{R}$ is H.

40. A compound of claim 38 in which one or both of R and R' in $-PO_3\mathbf{RR'}$, $-\mathbf{O}PO_3\mathbf{RR'}$, $-CH_2PO_3\mathbf{RR'}$, $-CF_2PO_3\mathbf{RR'}$, $-OCH_2CO_2\mathbf{R}$, $-NHCH_2CO_2\mathbf{R}$,

$-CH_2CO_2\mathbf{R}$, $-CF_2CO_2\mathbf{R}$, $-SO_3\mathbf{R}$, $-CH_2SO_3\mathbf{R}$, or $-CF_2SO_3\mathbf{R}$ is $-(M)_m-CH_2Z$, $-(M)_m-CHZ_2$, $-(M)_m-CZ_3$, $-R^{15}$, $-M-O-CO-R^{15}$ or $-M-O-CO-OR^{15}$, where Z is halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic.

41. A compound of claim 40 in which R^{15} is methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl.

42. A compound of claim 29 wherein $\mathbf{R}^6$ comprises $-APO_3\mathbf{RR'}$ or $-OPO_3\mathbf{RR'}$ and $\mathbf{R}^7$ is $-A-(M)_n-$ aliphatic or $-\mathbf{G}-(M)_n-$ aliphatic, where the aliphatic moiety is substituted or unsubstituted.

43. A compound of claim 36 or 42 wherein $\mathbf{R}^6$ comprises $-OPO_3H_2$.

44. A compound of claim 29 wherein $\mathbf{R}^6$ and $\mathbf{R}^7$ are independently selected from **J** and **K**.

45. A compound of claim 29 wherein $\mathbf{R}^6$ is $-C(\mathbf{R})(\mathbf{J})(\mathbf{K})$.

46. A compound of claim 45 wherein R is H.

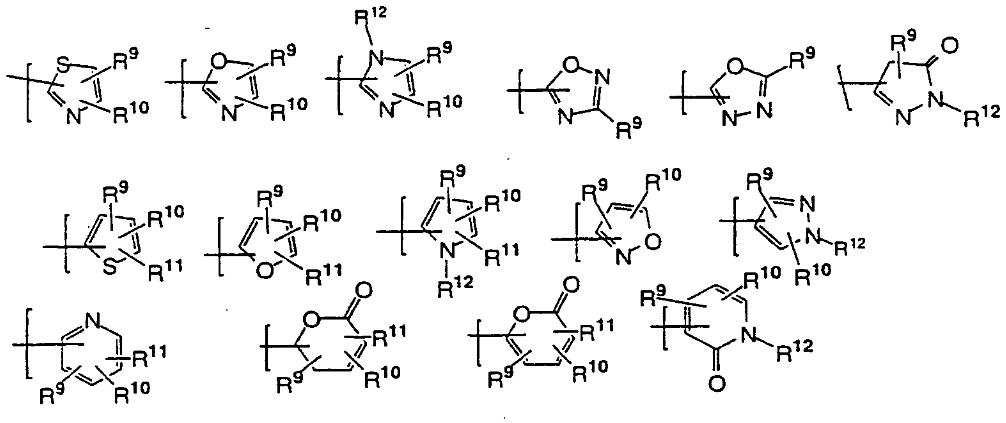
47. A compound of claim 45 or 46 wherein J is $-PO_3\mathbf{RR'}$.

48. A compound of claim 47 in which one or both of R and R' are H.

49. A compound of claim 47 in which one or both of R and R' are $\mathbf{R}^{15}$, $-(M)_m-CH_2Z$, $-(M)_m-CHZ_2$, $-(M)_m-CZ_3$, $-M-O-CO-R^{15}$ or $-M-O-CO-OR^{15}$, where Z is halogen and R^{15} is substituted or unsubstituted lower aliphatic, aryl or heterocyclic.

50. A compound of claim 49 in which R^{15} is methyl, ethyl, n–propyl, i–propyl, n–butyl, isobutyl, t–butyl, n–amyl, sec–amyl, benzyl or substituted benzyl.

51. A compound of claim 1–50, comprising a moiety **B** selected from the group consisting of:



wherein each of $\mathbf{R}^9$, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ is independently –$(\mathbf{M})_n\mathbf{Z}$, –$(\mathbf{M})_n\mathbf{R}$, –$(\mathbf{M})_n\mathbf{GR}$, –$(\mathrm{M})_n\mathrm{CN}$, –$(\mathbf{M})_n\mathbf{WR}$, or –$(\mathbf{M})_n\mathbf{WGR}$ (including, e.g., halo, R, –OR, –SR, –NRR', –COR,–$\mathrm{CO_2}$**R**, or –$(\mathbf{M})_n$**W–NRR'**), and,

$\mathbf{R}^{12}$ is independently selected from –$(\mathbf{M})_q\mathbf{Z}$, –$(\mathbf{M})_n\mathbf{R}$, –$(\mathbf{M})_q\mathbf{GR}$, –$(\mathbf{M})_n\mathbf{WR}$, and –$(\mathbf{M})_n\mathbf{WGR}$.

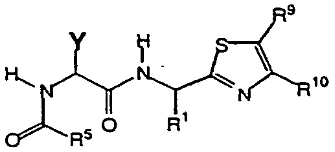
52. A compound of claim 51 wherein one or more of the **R**, **R'** and **R"** groups contains at least one substituent selected from halo, hydroxy, aliphatic, amino, amido and sulfonamido moieties.

53 . A compound of claim 51 wherein one or more of $\mathbf{R}^9$, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ is a substituted aliphatic moiety containing at least one substituent selected from substituted or unsubstituted cycloaliphatic, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, –$\mathrm{CO_2R}$, –CO–NRR', –COR, and –OR.

54. A compound of claim 51, wherein one or more of $\mathbf{R}^9$, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ comprises –$(\mathrm{M})_n$(cycloaliphatic), –$(\mathrm{M})_n$(substituted or unsubstituted aryl), –$(\mathrm{M})_n$(substituted or unsubstituted heteroaryl), –$(\mathrm{M})_n\mathrm{CHO}$, –$(\mathrm{M})_n\mathrm{CONH_2}$, –$(\mathrm{M})_n\mathrm{CSNH_2}$, –$(\mathrm{M})_n\mathrm{SONH_2}$,–$(\mathrm{M})_n\mathrm{SO_2NRR'}$, –$(\mathrm{M})_n\mathrm{OR}$, –$(\mathrm{M})_n$(lower aliphatic), –$(\mathrm{M})_n$–C(OR)R'R'', or –$(\mathrm{M})_n$–C=CRR'.

55. A compound of claim 51, wherein one or more of $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, and $\mathbf{R^{12}}$ comprises methyl, $-(CH_2)_q R^{13}$ where q is 1–8 and R^{13} comprises methyl; i–propyl; i–butyl; t–butyl; cycloaliphatic; phenyl; substituted phenyl; naphthyl; substituted naphthyl; a 5, 6 or 7–membered heterocyclic ring or a bicyclic heterocylic moiety.

56. A compound of claim 1 of the formula:



57. A compound of claim 56 in which $\mathbf{R^9}$ is H; a linear, branched or cyclic lower aliphatic; $-(M)_n$OR, $-(M)_n$COOR, or $-(M)_n$CONRR'.

58. A compound of claim 57 in which one or more **R** groups of $\mathbf{R^9}$ are H;

59. A compound of claim 56 - 58 in which **n** in $\mathbf{R^9}$ is 0, 1 or 2, and/or each **M** in $\mathbf{R^9}$ is CH_2.

60. A compound of any of claims 56 - 59 in which $\mathbf{R^1}$ is H, lower aliphatic (which may be branched, unbranched or cyclic), $-(M)_n$OR, $-(M)_n$COOR, $-(M)_n$CONRR', $-(M)_n$aryl or $-(M)_n$heterocyclic.

61. A compound of claim 60 in which each **M** of $\mathbf{R^1}$ is CH_2; **n** is 1, 2 or 3; and/or one or more R groups of $\mathbf{R^1}$ is H.

62. A compound of any of claims 56 - 61 in which $\mathbf{R^5}$ is a linear, branched or cyclic lower aliphatic moiety.

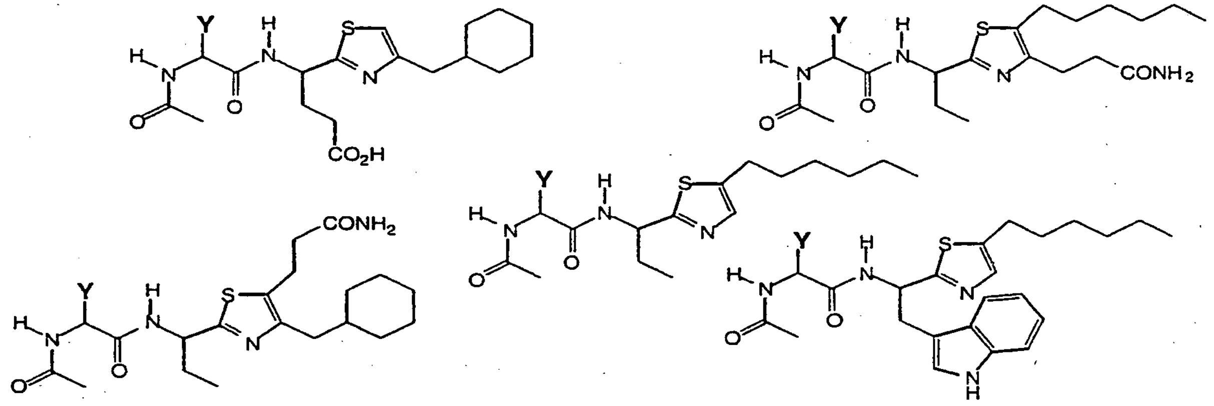
63. A compound of any of claims 56 - 62 in which $\mathbf{R^{10}}$ is H, $-M_n$–branched, unbranched or cyclic aliphatic, $-(M)_n$OR, $-(M)_n$COOR, or $-(M)_n$CONRR'.

64. A compound of claim 63 in which each **M** moiety in $\mathbf{R}^{10}$ is CH_2.

65. A compound of claim 63 or 64 in which **n** in $\mathbf{R}^{10}$ is 0, 1, 2 or 3.

66. A compound of claim 63 - 65 in which one or more **R** groups in $\mathbf{R}^{10}$ is H.

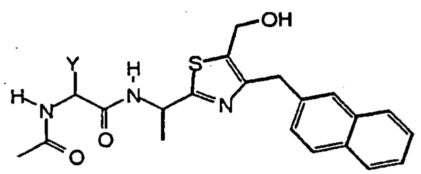
67. A compound of claim 56, selected from the set consisting of:

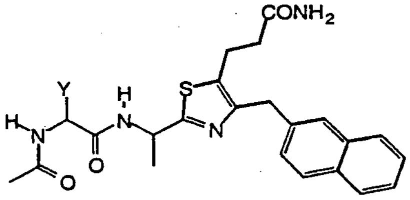


68. A compound of any of claims 56 - 62 in which $\mathbf{R}^{10}$ is $-\mathbf{M}_n$–aryl or $-\mathbf{M}_n$–heterocyclic, where the aryl or heterocyclic moiety may be substituted or unsubstituted.

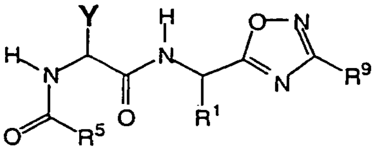
69. A compound of claim 68 in which each **M** of $\mathbf{R}^{10}$ is CH_2 and/or **n** is 1, 2 or 3.

70. A compound of claim 68 selected from the set consisting of:





71. A compound of claim 1 of the formula:



72. A compound of claim 71 wherein $\mathbf{R^5}$ comprises a substituted or unsubstituted lower aliphatic moiety, which may be branched, unbranched or cyclic.

73. A compound of claim 71 or 72 wherein $\mathbf{R^1}$ is H, lower aliphatic (which may be branched, unbranched or cyclic), $-(M)_n$OR, $-(M)_n$COOR, $-(M)_n$CONRR', $-(M)_n$aryl or $-(M)_n$heterocyclic, wherein the aryl or heterocyclic moiety may be substituted or unsubstituted.

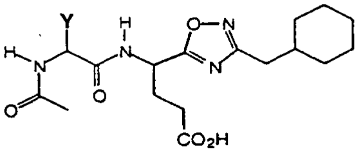
74. A compound of claim 73 in which each **M** of $\mathbf{R^1}$ is CH_2; **n** is 1, 2 or 3; and/or one or more R groups of $\mathbf{R^1}$ is H.

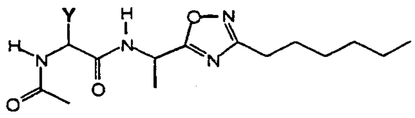
75. A compound of claim 71 - 74 in which $\mathbf{R^9}$ comprises H or a substituted or unsubstituted lower aliphatic moiety.

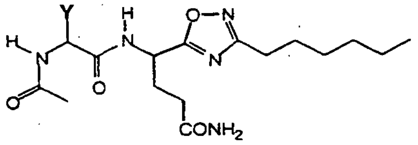
76. A compound of claim 71 - 74, wherein $\mathbf{R^9}$ comprises a linear, branched or cyclic lower aliphatic; $-(M)_n$COOR; $-(M)_n$CONRR'; or $-(M)_n$cycloaliphatic, in which the aliphatic or cycloaliphatic moiety is substituted or unsubstituted.

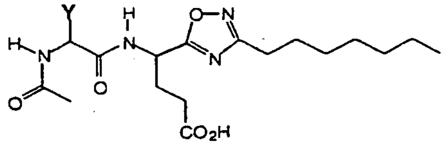
77. A compound of claim 76 in which each **M** of $\mathbf{R^9}$ is CH_2; and/or **n** is 0, 1, 2 or 3.

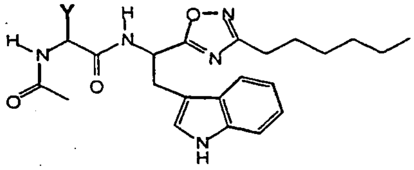
78. A compound of claim 71, selected from the group consisting of:

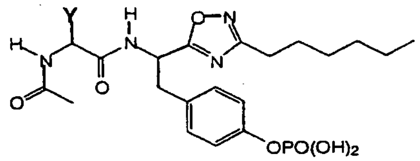








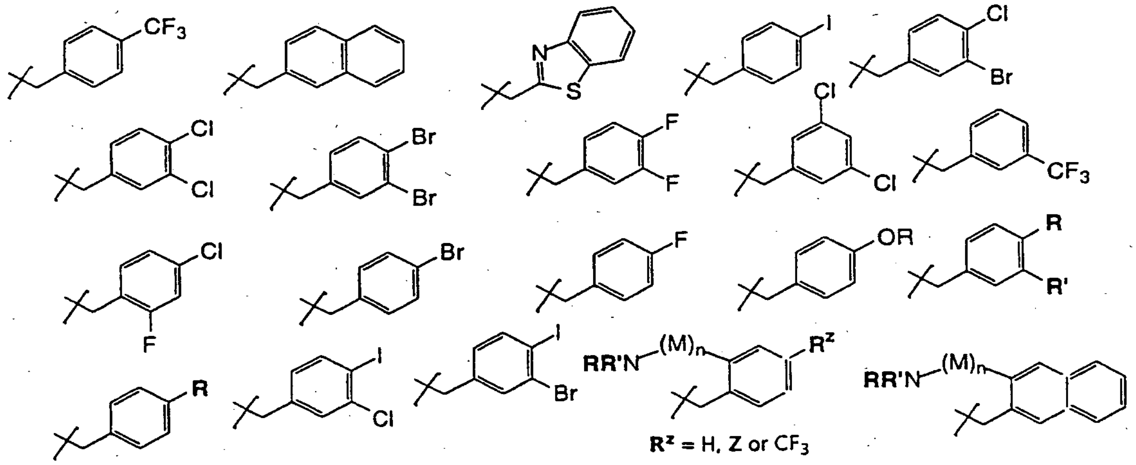




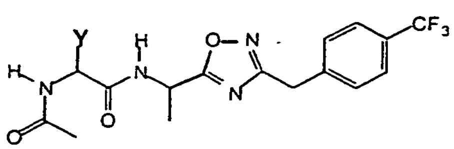
79. A compound of claim 71 - 74, wherein $\mathbf{R^9}$ comprises $-(\mathbf{M})_n$aryl or $-(\mathbf{M})_n$heterocyclic, in which the aryl and heterocyclic moiety may be substituted or unsubstituted.

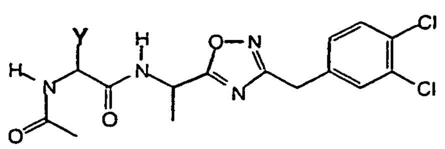
80. A compound of claim 79 in which each **M** of $\mathbf{R^9}$ is CH_2; and/or **n** is 0, 1, 2 or 3.

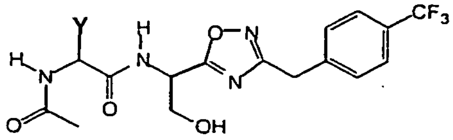
81. A compound of claim 80, wherein $\mathbf{R^9}$ is selected from the group consisting of:

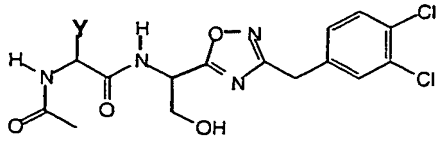


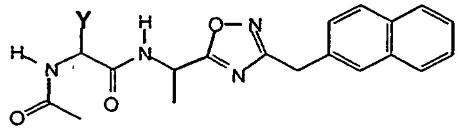
82. A compound of claim 71, selected from the group consisting of:

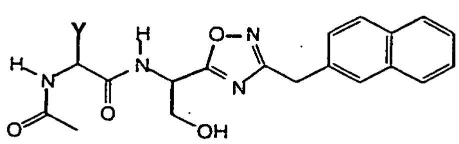


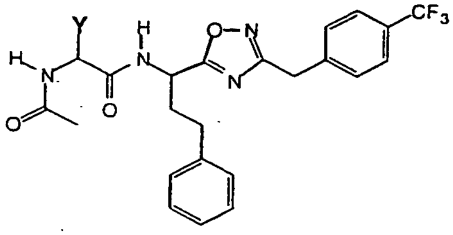


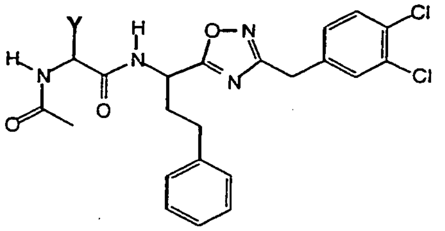




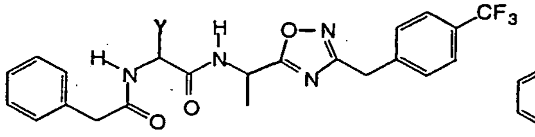


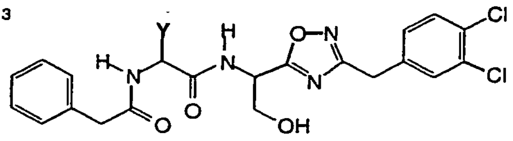


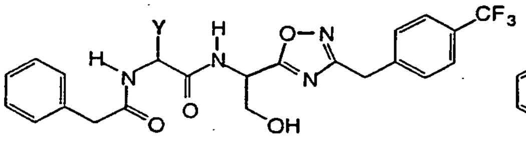


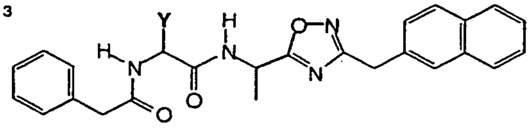


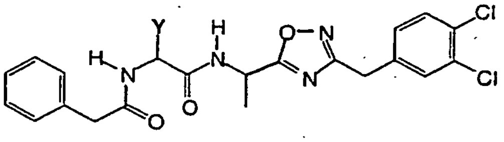
83. A compound of claim 71, selected from the group consisting of:

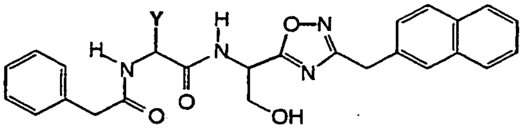




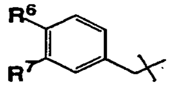




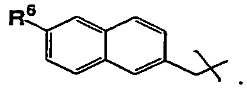




84. A compound of any of claims 51 to 83, containing a Y moiety comprising:



or



where R^6 comprises $-PO_3RR'$, $-OPO_3RR'$, $-MPO_3RR'$, $-SO_2NRR'$, $-OSO_2NRR'$, $-ACO_2R$, $-A$-tetrazole, or $-CRJK$.

85. A compound of claim 84, wherein $\mathbf{R^6}$ comprises $-PO_3RR'$.

86. A compound of claim 84, wherein $\mathbf{R^6}$ comprises $-OPO_3RR'$.

87. A compound of claim 84, wherein $\mathbf{R^6}$ comprises $-CH_2PO_3RR'$.

88. A compound of claim 84, wherein $\mathbf{R^6}$ comprises $-CF_2PO_3RR'$.

89. A compound of claim 84, wherein $\mathbf{R^6}$ comprises $-OCH_2PO_3RR'$.

90. A compound of claim 84, wherein $\mathbf{R^6}$ comprises –COOR or –tetrazole.

91. A compound of claim 84, wherein $\mathbf{R^6}$ comprises $-OCH_2COOR$ or $-OCH_2$tetrazole.

92. A compound of claim 84, wherein $\mathbf{R^6}$ comprises –CHJK or –CZJK.

93. A compound of claim 92, wherein **J** and **K** are independently selected from the group consisting of $-PO_3RR'$, –COOR, and $-SO_2NRR'$.

94. A compound of any of claims 84 - 93 wherein $\mathbf{R^7}$ comprises R,–CN, $-NO_2$, halogen, **J**, $-\mathbf{A}-(\mathbf{M})_n$aliphatic, $-\mathbf{G}-(\mathbf{M})_n$aliphatic , $-(\mathbf{M})_nCOCF_3$, $-(\mathbf{M})_nOH$, $-(\mathbf{M})_nCOOR$, $-\mathbf{A}-(\mathbf{M})_n\mathbf{NRR'}$, $-\mathbf{G}-(\mathbf{M})_n\mathbf{NRR'}$, $-(\mathbf{M})_nCHO$, $-\mathbf{A}-(\mathbf{M})_nN(R)(CO)R'$, $-\mathbf{G}-(\mathbf{M})_nN(R)(CO)R'$, $-\mathbf{A}-(\mathbf{M})_n-CO-\mathbf{NRR'}$, or $-\mathbf{G}-(\mathbf{M})_n-CO-\mathbf{NRR'}$, where the aliphatic groups may be substituted or unsubstituted; or $\mathbf{R^7}$ is a covalent bond to an $\mathbf{R^4}$ substituent of **X** to form an aliphatic, aryl or heterocyclic ring of 4 to 8 atoms.

95. A compound of claim 94 wherein $\mathbf{R^7}$ comprises H, lower alkyl, lower alkenyl or –CHO.

96. A compound of claim 94 wherein $\mathbf{R^7}$ comprises J.

97. A compound of any of claims 84 to 94 wherein one or more R groups (including R', R", etc) of $\mathbf{R^6}$ or $\mathbf{R^7}$ comprise $-(M)_m-CH_2Z$, $-(M)_m-CHZ_2$, $-(M)_m-CZ_3$, $-R^{15}$, $-M-O-CO-R^{15}$ or $-M-O-CO-OR^{15}$, where Z is halogen and R^{15} is a substituted or unsubstituted lower aliphatic, aryl or heterocyclic group.

98. A compound of any of claims 84 to 94 wherein one or more R groups (including R', R", etc) of $\mathbf{R^6}$ or $\mathbf{R^7}$ comprise H.

99. A compound of any of claims 1–98 which binds to a given SH2 domain with a IC_{50} value of less than about 50 μM.

100. A compound of claim 99, which binds to a given SH2 domain with a IC_{50} value of less than about 20 μM.

101. A compound of claim 99 wherein the SH2 domain is from a Src, Fyn, Lck, Yes, Blk, Lyn, Fgr, Hck, Yrk, ZAP-70, Syk, STAT or Abl protein.

102. A composition comprising a compound of any of claims 1–101, or a pharmaceutically acceptable derivative thereof; and a pharmaceutically acceptable excipient.

103. A method for inhibiting SH2–mediated signal transduction in a mammal in need thereof which comprises administering to the mammal a composition of claim 102.

104. The method of claim 103, wherein the composition contains a compound which specifically binds to an SH2 domain of Src, ZAP–70, Syk, or STAT 6.

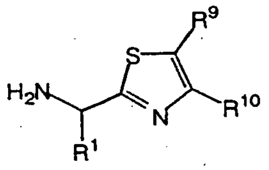
105. The method of claim 103, wherein said SH2–mediated signal transduction is mediated by a PDGF receptor protein, EGF receptor protein, HER2/Neu receptor protein, fibroblast growth factor receptor protein, focal adhesion kinase protein, p130 protein, or p68 protein.

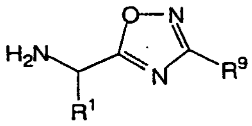
106. The method of claim 103, wherein the mammal has a proliferative disease, cancer, restenosis, osteoporosis, inflammation, allergies, or cardiovascular disease.

107. A method of treating or preventing a proliferative disease, cancer, restenosis, osteoporosis, inflammation, allergic reaction, or cardiovascular disease in a patient, the method comprising administering to the patient a therapeutically effective amount of a composition of claim 102.

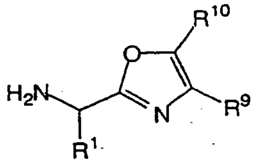
108. A method for inducing immunosuppression in a patient, the method comprising administering to the patient an amount of a composition of claim 102 sufficient to cause immunosuppression.

109. A compound of having a structure selected from the group consisting of:





and



wherein each of $\mathbf{R^9}$ and $\mathbf{R^{10}}$ is independently $\mathbf{-(M)_nZ}$, $\mathbf{-(M)_nR}$, $\mathbf{-(M)_nGR}$, $\mathbf{-(M)_nWR}$, or $\mathbf{-(M)_nWGR}$ (including, e.g., halo, **R**, **–OR**, **–SR**, **–NRR'**, **–COR**,$\mathbf{-CO_2R}$, or $\mathbf{-(M)_nW\text{–}NRR'}$).

INTERNATIONAL SEARCH REPORT

Inte: inal Application No
PCT/US 99/05970

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F9/6539 A61K31/675 C07F9/653 C07F9/6558 C07F9/58 C07F9/6553 C07F9/655 C07D271/06 A61K31/33 C07D413/06 C07D417/06 C07D277/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 12903 A (WARNER-LAMBERT CO.) 10 April 1997 see the whole document ---	1-108
Y	STANKOVIC C J ET AL: "The role of 4-phosphonodifluoromethyl- and 4-phosphono-phenylalanine in the selectivity and cellular uptake of SH2 domain ligands" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 14, 22 July 1997, page 1909-1914 XP004136356 see the whole document --- -/--	1-108

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 27 May 1999	Date of mailing of the international search report 10/06/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Beslier, L

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	MARK S. PLUMMER: "Design, synthesis, and cocrystal structure of a nonpeptide Src SH2 domain ligand" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 23, 7 November 1997, pages 3719-3725, XP002095199 WASHINGTON US see the whole document ---	1-108
Y	WO 97 31016 A (ARIAD PHARMACEITICALS, INC.) 28 August 1997 see the whole document ---	1-108
Y	ELIZABETH A. LUNNEY: "Structure-based design of a novel series of nonpeptide ligands that bind to the pp60src SH2 domain" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 51, 24 December 1997, pages 12471-12476, XP002095200 DC US see the whole document ---	1-108
X	GB 1 284 379 A (ISTITUTO FARMACOLOGICO SERONO S.P.A.) 9 August 1972 see claim 1; example 2 ---	109
X	US 4 123 541 A (SHO INOUE) 31 October 1978 see tables I,III ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103856 see BRN=4889252 & HETEROCYCL.CHEM., vol. 28, no. 5, 1991, pages 1241-1244, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103857 see BRN=7520751 & J.MED.CHEM., vol. 39, no. 4, 1996, pages 968-981, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103858 see BRN=744937 & GAZZ.CHIM.ITAL., vol. 93, 1963, pages 1196-1205, ---	109

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beistein Informationssysteme Gmbh Frankfurt DE XP002103859 see BRN=4965961 & LIEBIGS ANN. CHEM., vol. 10, 1986, pages 1749-1764, ---	109
X	DATABASE CROSSFIRE Beilstein informationssysteme Gmbh Frankfurt DE XP002103860 see BRN=5412066 & J.MED.PHARM.CHEM., vol. 4, no. 2, 1961, pages 351-367, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103861 see BRN=6637182 & EUR.J.MED.CHEM.CHIM.THER., vol. 28, no. 10, 1993, pages 801-810, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103862 see BRN=107868 & J.AMER.CHEM.SOC., vol. 72, 1950, pages 4526-4528, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103863 see BRN=108572 and BRN=113632 & J.CHEM.SOC.,1947, pages 1372-1373, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103864 see BRN=136236 & J.AMER.CHEM.SOC., vol. 79, 1957, pages 4524-4527, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103865 see BRN=750414 and BRN=143590 & JUSTUS LIEBIGS ANN.CHEM., vol. 676, 1964, pages 141-150, --- -/--	109

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103866 see BRN=509752 & J.AMER.CHEM.SOC., vol. 86, 1964, pages 2478-2490, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103867 see BRN=744560 and BRN=970544 & J.CHEM.SOC.,1960, pages 925-931, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103868 see BRN=985991 & J.CHEM.SOC.,1966, pages 2115-2119, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103869 see BRN=1116624 & JUSTUS LIEBIGS ANN.CHEM.,1975, pages 410-414, ---	109
X	DATABASE CROSSFIRE Beilstein Informationssysteme Gmbh Frankfurt DE XP002103870 see BRN=4920318 & BULL.CHEM.SOC.JPN., vol. 47, 1974, pages 151-155, -----	109

INTERNATIONAL SEARCH REPORT

I .national application No.
PCT/US 99/05970

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 103-108
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 103-108
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 99/05970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9712903 A	10-04-1997	AU 7392696 A	28-04-1997
WO 9731016 A	28-08-1997	AU 2277597 A	10-09-1997
GB 1284379 A	09-08-1972	CH 554360 A	30-09-1974
		DE 2108437 A	11-11-1971
		FR 2081532 A	03-12-1971
		JP 50004662 B	22-02-1975
		US 4020082 A	26-04-1977
US 4123541 A	31-10-1978	JP 52097964 A	17-08-1977
		JP 52105185 A	03-09-1977
		DE 2705875 A	18-08-1977
		FR 2340944 A	09-09-1977
		GB 1527483 A	04-10-1978
		US 4101660 A	18-07-1978

Form PCT/ISA/210 (patent family annex) (July 1992)